Title: Effectiveness of interventions to identify and manage patients with familial cancer risk in primary care: a systematic review

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Figures & Tables
1. Figure1: PRISMA flow diagram
2. Table 1: Summary description of included studies
3. Table 2: GRADE evidence profile
4. Table 3: Risk of bias table

Supplementary materials
1. Search strategy
2. Excluded studies
3. Outcome table
4. Studies excluded for having patients with personal history of cancer

Keywords
Primary health care, genetic predisposition to disease, breast neoplasm, ovarian neoplasms, colorectal neoplasms, prostatic neoplasms

ABSTRACT

This systematic review evaluated the effectiveness of strategies to identify and manage patients with familial risk of breast, ovarian, colorectal and prostate cancer in primary care to improve clinical outcomes. MEDLINE, EMBASE, CINAHL and Cochrane library were searched from January 1980 to October 2017. We included randomised controlled trials (RCT) and non-randomised studies of interventions (NRSI). Primary outcomes were cancer incidence, cancer related clinical outcomes or identification of cancer predisposition; secondary outcomes were appropriateness of referral, uptake of preventive strategies, cognitive and psychological effect. From 11842 abstracts, 111 full texts were reviewed and three eligible studies (nine articles) identified. Two were cluster RCTs and one NRSI; all used risk assessment software. No studies identified our primary outcomes, with no consistent outcome across the three studies. In one RCT, intervention improved the proportion of genetic referrals meeting referral guidelines for breast cancer (OR 4.5, 95% CI 1.6 to 13.1). In the other RCT, there was no difference in screening adherence between the intervention and control group. However, there was borderline increased risk perception (OR 1.89, 95% CI 0.99 to 3.59) in the subgroup that under-estimated their colon cancer risk. In the NRSI, there was no change in psychological distress in patients at increased familial breast cancer risk, but population risk patients had reduced anxiety after intervention (state anxiety mean change –3, 95% CI -5 to -2). Future studies should have better defined comparator groups, longer follow up, and assess outcomes using validated tools.

242 words

INTRODUCTION

Familial cancer risk increases an individual's life time chance of developing cancer and at an earlier age of onset (Kerber et al. 2005; Paluch-Shimon et al. 2016; Qureshi et al. 2009). A Swedish Cancer Registry study found that cancers with the highest familial proportions (proportion of cases with affected parents/siblings) were prostate, breast and colorectal cancer (Hemminki et al. 2008). As well as being the most common cancers worldwide, they are associated with the commonest cancer related gene mutations (Qureshi et al. 2007; World Cancer Research Fund). For instance, BRCA1 mutations increase the risk of breast, ovarian and prostate cancer, whilst DNA mismatch repair gene mutations are associated with Lynch Syndrome (Qureshi et al. 2007).

Familial cancers are usually divided into three categories. For example, the English National Institute for Health and Care Excellence (NICE) categorised breast cancer risk into: at or near population (<17% lifetime risk), moderate (17% to 29%) and high risk (>30%) (NICE 2017). A 2005 California population survey reported the prevalence of strong and moderate familial cancer risk to be 5% and 7% for breast, 1% and 5% for colorectal and prostate cancer. This risk stratification was based on the proximity of affected relatives and age at cancer diagnosis (Scheuner et al. 2010).

As illustrated above, the definition of familial cancer risk varies in different countries and guidelines. Nevertheless, high risk generally indicates probability of single gene disorder with Mendelian inheritance (Duffy et al. 2013; Qureshi et al. 2007; Scheuner et al. 2010). Conversely, moderate risk may be due to combinations of multiple low penetrance gene mutations with or without shared environmental or behavioural risk factors (Qureshi et al. 2007).

Preventive measures such as surveillance, prophylactic surgery or chemoprevention can reduce cancer incidence and mortality for patients with familial cancer risk (Carbine et al. 2018; Cuzick et al. 2013; Domchek et al. 2010; Duffy et al. 2013). A Cochrane review found that bilateral risk reducing mastectomy decreased breast cancer incidence and death, particularly in women with BRCA 1/2 mutations (Carbine et al. 2018). The FH01 study estimated that annual mammogram for women aged 40-49 with moderate familial breast cancer risk (defined as at least 3% risk for this age group) reduced breast cancer mortality by 40% (Duffy et al. 2013). In a 15-year controlled trial, colonoscopy screening at three-year intervals reduced the colorectal cancer rate by 62% and overall mortality by 65% in families with Lynch Syndrome (Järvinen et al. 2000).

For at-risk patients to benefit from these preventive measures, primary care providers play a crucial role. To assess familial cancer risk, primary care providers need to collect a family history, the English NICE guideline suggests using family history tools to collect comprehensive family histories (NICE, 2017). Clinical decision support systems can then be used to translate this information into risk strata with evidence-based recommendation on appropriate management, e.g. referral to genetic services for those at high familial risk or reassurance of patients at near population risk (NICE, 2017; Paluch-Shimon et al. 2016; U.S. Preventive Services Task Force, 2015).

However, it is still unclear if familial cancer risk assessment and management in primary care improves clinically relevant outcome, such as cancer morbidity and mortality. Previous systematic reviews focused on the impact of multifactorial cancer risk assessment tools, the validity of family history tools, specialist risk assessment

services and familial breast cancer only (Cleophat et al. 2018; Hilgart et al. 2012; Qureshi et al. 2009; Walker et al. 2015).

The current systematic review focused on the effectiveness of primary care interventions to identify and manage patients at familial cancer risk, to improve clinical outcomes for breast, ovarian, prostate and colorectal cancers. This will help policy makers decide which familial cancer risk assessment interventions are worth adopting and help researchers identify the gaps in evidence.

METHODS

The Cochrane Collaboration's guidance on review of interventions and the PRISMA-P checklist were followed (Higgins et al. 2011b; Shamseer et al. 2015). The protocol was registered on PROSPERO in December 2017 (PROSPERO 2017).

Literature search

Databases searched were: MEDLINE, EMBASE, CINAHL, and Cochrane library. Aligned with the introduction of familial cancer clinics in the late 1980s, the search period was from 1st Jan 1980 to 4th October 2017 (Hilgart et al. 2012). We used controlled vocabulary and free text terms based on the concepts of 'cancer: breast, ovarian, colorectal and prostate', 'familial/hereditary cancer', and 'primary health care'.

With the Zetoc database, we also searched the table of contents within the last five years for: Journal of Community Genetics, European Journal of Human Genetics, Genetics in Medicine, and Public Health Genomics. Other searches included clinical trial registries (U.S. National Institutes of Health (www.clinicaltrials.gov), ISRCTN registry, WHO International Clinical Trials Registry Platform), The Networked Digital Library of Theses and Dissertations, the conference proceedings within the last five years for

European Society of Human Genetics Conference and American College of Medical Genetics and Genomics annual meetings, and the reference list of included studies. See supplementary material 1 for full details of the search strategy.

Study selection

Two authors screened the titles and abstracts (SL and MP/BD) and full texts (SL and MP) independently. Discrepancies were resolved with a third author (NQ). Authors of studies were contacted where clarification were required.

Studies were eligible if published in English and evaluated an intervention that identified and managed patients at risk of familial breast, ovarian, colorectal or prostate cancer. Data must have been presented separately for each cancer type, except breast and ovarian cancer, as BRCA1/2 associated breast and ovarian cancer is a recognised hereditary cancer syndrome (Petrucelli et al. 2010). Randomised controlled trials (RCT) and non-randomised studies for intervention (NRSI) were eligible. Reviews, genetic epidemiology studies with no clinical intervention, stand-alone guidelines, case reports, editorials, qualitative studies, abstracts and studies with no comparator arm were excluded.

Participants included were adults aged >18 with no previous history of cancer or known cancer genetic mutation. The intervention must have been based in primary care or non-specialist community health service and care managed by primary care providers. We defined primary care providers as health professionals who delivered care to undifferentiated patients as the first contact point in the community. This could be a general practitioner (family doctor or family physician), internal medicine physician, or obstetrician/ gynaecologist practising in the community (Qureshi et al. 2007).

The primary outcomes were cancer incidence; cancer related morbidity, mortality and survival; and identification of cancer predisposition (increased familial risk) as defined by study authors. Secondary outcomes were appropriateness of specialist referrals (as defined by study authors); uptake of preventive strategies; cognitive and psychological effect measured with validated tools.

Data extraction and analysis

Data on study characteristics and pre-specified outcomes were extracted by two reviewers independently (SL and BD/JL) using standardised forms and discrepancies resolved with a third author (NQ). Where there were multiple publications from the same study, the data were grouped together and treated as a single study (Higgins et al. 2011b).

Quality assessment

Two authors reviewed the risk of bias for the included studies independently (SL and NQ/SW) with discrepancies resolved with a third author (SW/NQ). The Cochrane Collaboration Risk of Bias tool was used for RCT, and the ROBINS-I tool was used for NRSI (Higgins et al. 2011a; Sterne et al. 2016). The GRADE approach was used to rate the certainty of evidence for the included outcomes (Schünemann et al. 2013).

RESULTS

From the initial 11842 titles and abstracts, we screened 111 full texts for eligibility (figure 1). Three studies comprising nine articles were included (Emery et al. 2007; Family Healthware Trial (O'Neil et al. 2009; Acheson et al. 2010; Rubinstein et al. 2011a; Rubinstein et al. 2011b; Ruffin et al. 2011; Wang et al. 2012; Wang et al. 2015); Van Erkelens et al. 2017). Only four outcomes were identified. No studies reported the

same outcomes. Three further studies were identified that are ongoing or awaiting publication (ISRCTN 2014; Naicker et al. 2013; Voils 2017). Supplementary material 2 presents the table of excluded studies with reasons for exclusion.

Due to the limited number of included studies with varying study designs and study interventions, meta-analysis was not feasible. The outcomes were presented as a narrative summary. See supplementary material 3 for further details.

Included studies

Table 1 summarised the characteristics of the three included studies. Of these, two were cluster RCTs (Emery et al. 2007; Family Healthware Trial) and one NRSI (uncontrolled before and after study) (Van Erkelens et al. 2017). Two studies were based in Europe and one in the USA. Two studies evaluated interventions for breast, ovarian and colorectal cancer, and one study for breast cancer only. Follow up duration ranged from 2 weeks to 12 months, with a median follow up time of 6 months. The average age of patients ranged from 51 to 56. Patients were predominantly white, female, and college educated.

All three studies used a bespoke software for familial cancer risk assessment: a clinician pedigree drawing tool based on patient completed family history questionnaire (Emery et al. 2007), a patient facing familial risk assessment tool online or via telephone interview (Family Healthware Trial), and a patient online self-test (Van Erkelens et al. 2017). All three subsequently generated a risk based action plan: one informed general practitioners who needed genetic referral (Emery et al. 2007), another provided personalised familial risk assessment outcome and prevention plan for patients and all types of primary care providers (Family Healthware Trial), and the final study advised

patients with increased risk to consult their primary care providers (unspecified health care professionals) (Van Erkelens et al. 2017).

Two studies used a proactive approach by screening all patients with an upcoming appointment with their primary care provider (Family Healthware Trial) or attending population-based breast cancer screening (Van Erkelens et al. 2017). One study employed a reactive approach and only conducted a familial risk assessment when approached by patients concerned about their cancer family history (Emery et al. 2007).

Primary outcome

No studies identified the review's primary outcome (cancer incidence, cancer related morbidity, mortality, survival, or identification of cancer predisposition). Although the Family Healthware Impact Trial reported the characteristics of patients with interim cancer diagnosis during the six month follow up period (five intervention and two control patients reported a new breast cancer diagnosis; 17 intervention and 10 control patients reported 'other' cancer; none reported colon or ovarian cancer diagnosis), the authors excluded these patients from the analyses of screening adherence as it was not clear whether the tests or consultations were performed for screening or diagnostic purposes during the intervention period (Rubinstein et al. 2011a).

Secondary outcome

None of the three studies reported the same outcomes. The four secondary outcomes reported were: appropriateness of specialist referrals, uptake of preventive strategies, patients' self-reported risk perception and patients' self-reported anxiety and depression. Details of each outcome were described below. Using the GRADE approach, these

outcomes had *low* to *very low* certainty of evidence (table 2). This is driven by weakness in the study design, leading to risk of bias (see risk of bias section).

I. Appropriateness of specialist referrals

Emery et al.'s cluster RCT showed that the use of a risk assessment and decision support software resulted in significantly higher proportion of general practitioners' referral letters meeting the referral guidelines for breast cancer (93% intervention vs 73% control, OR 4.5, 95% CI 1.6 to 13.1) but not for colorectal cancer (99% vs 92%, OR 6.5, 95% CI 0.5 to 83.7) (2007).

After specialist review at the genetic clinic, the proportion of general practitioners' referrals that were confirmed as increased risk was similar for intervention and control for breast cancer (77% vs 70%, OR 1.4, 95% CI 0.6 to 3.5). In contrast, for colorectal cancer, the proportion assessed to be at increased risk by the specialist was lower in the intervention arm (56% vs 85%, OR 0.2, 95% CI 0.1 to 0.8) (Emery et al. 2007).

II. Uptake of preventive strategies

The Family Healthware cluster RCT found that six months post-intervention, there was no significant difference in improved adherence between the intervention and control arm for risk-based mammography (improvement in adherence, 9% intervention vs 7% control, p=0.82) and colorectal cancer screening (8% vs 7%, p=0.95). This was also the case for the subgroup of patients who were not adherent at baseline. During the intervention period, there was no difference between study arm in the number of women receiving CA-125 blood test and transvaginal ultrasound for ovarian cancer risk (supplementary material 3) (Rubinstein et al. 2011a).

III. Cognitive effect: Patients' risk perception

The Family Healthware trial did not report this outcome for all patients. However, in the subgroup of patients who under-estimated their risk, more of the intervention patients' risk perception became consistent with their risk status at six months for colorectal cancer, although this was of borderline significance (17% vs 10%, OR 1.89, 95% CI 0.99 to 3.59). This was not observed for breast or ovarian cancer (Rubinstein et al. 2011a).

IV. Psychological effect: Patients' anxiety & depression

Van Erkelens et al.'s NRSI used the State-Trait Anxiety Inventory (STAI) and Hospital Anxiety and Depression Scale (HADS). The analysis of the total study population was not presented. Subgroup analysis by risk status was provided: women told to be at *population risk* for breast cancer had reduced anxiety immediately after self-risk assessment (mean change of state anxiety -2, 95% CI -2 to -1) and at two weeks (-3, 95% CI -5 to -2). The HADS score remained unchanged at two weeks. For women at *increased breast cancer risk*, there was no consistent change in anxiety and depression (table 2). The mean score for STAI and HADS were below the levels of clinical significance and similar to those of the general population (supplementary material 3) (2017).

Risk of bias

All three included studies were at high risk of bias (table 3). For Emery et al.'s cluster RCT, allocation concealment, blinding of participants and clinicians were not possible. The patient's non-attendance at the genetic clinic was 28% (45/162) for intervention and 38% (32/84) for control, contributing to attrition bias. Responder bias was evident from the 74% (125/170) practices that declined to participate. The author commented that this

recruitment rate is consistent with similar primary care trials and that practices that were interested in genetic medicine were more likely to participate (2007).

The Family Healthware trial had no description of the random sequence generation or allocation concealment. From the published study design, there appeared to be no blinding. The participant recruitment rate was low (18%) with high attrition: 20% intervention (542/2650) and 20% control (324/1598) participants withdrew from consent to follow up. Results for the change in risk perception was only reported for the subgroup who under-estimated their risk. Selection of participants who were free of comorbidities led to healthy volunteer bias. The lengthy baseline questionnaire may have altered the behaviour in the control group, reducing the intervention effect.

In Van Erkelen's NRSI, there was no control of the confounders such as age and sociodemographic factors. Finally, 35% (101/287) of patients at baseline were lost to follow up (2017).

Excluded studies: patients with a personal history of cancer

Two studies were excluded for having participants with a personal history of cancer but met other eligibility criteria: one cluster RCT and one before after study (supplementary material 4) (Wilson et al. 2005; Wilson et al. 2006; Orlando et al. 2011; Orlando et al. 2013; Wu et al. 2013; Orlando et al. 2014; Orlando et al. 2016). Overall, there were four (22/588) to eight percent (23/282) of participants with personal history of cancer. Similar to the main review, the secondary outcomes reported were: appropriateness of referrals and uptake of preventive strategies. However, the findings were different from the main review: intervention had no impact on the appropriateness of genetic referrals (Wilson et al. 2005; Wilson et al. 2006), but there was improved preventive uptake of

surveillance (breast magnetic resonance imaging) and gynaecology assessment for ovarian cancer screening (supplementary material 3) (Orlando et al. 2016).

DISCUSSION

Main findings

This is a comprehensive systematic review on the long-term clinical impact of primary care assessment and management of patients with familial breast, ovarian, prostate and colorectal cancer risk. Our review spanned the past 37 years and identified three studies. None of these studies assessed the review's primary outcome: cancer incidence, morbidity, mortality, survival or identification of cancer predisposition. The follow up period (two weeks to 12 months) would have been too short to identify the primary outcomes. For instance, a large community cohort study estimated that a period of five years is required for 1000 colorectal cancer cases to be identified from a sample size of 500 000 recruits (UK Biobank 2007).

The secondary outcomes predominantly evaluated short term outcomes of process and psychological measures; these evidence were of limited quality due to weakness in the study design. The strongest evidence emerged from a cluster RCT, demonstrating improved appropriateness of general practitioners' genetic referral letters for patients at familial breast cancer risk. However, this still had a low GRADE level of certainty (Emery et al. 2007).

Comparison with previous systematic review

To our knowledge, no systematic review has evaluated the clinical impact of familial cancer risk assessment and management by non-specialist primary care providers in primary care settings. The previous four reviews covered broader areas of multifactorial

cancer risk assessment tools, the validity and nature of cancer family history tools and familial breast cancer risk assessment by genetic services (Cleophat et al. 2018; Hilgart et al. 2012; Qureshi et al. 2009; Walker et al. 2015). All of these reviews shared some similar findings to the current review.

Walker et al. reviewed RCTs that evaluated the impact of cancer risk assessment tools in primary care. They identified 11 trials compared to three trials in our review, as we focused on familial cancer risk assessment, limited the types of cancer to those known to have a genetic component, grouped papers from the same study as a single trial and included only outcomes measured with validated tools. Despite focusing on familial cancer, our review findings were consistent with Walker et al.'s, specifically, there is limited evidence available on the effectiveness of cancer risk assessment on the uptake of screening and risk assessment does not increase psychological distress (2015).

Two reviews identified between 18 to 29 cancer family history tools used in primary care; a third of the tools provided risk stratification and action plan for patients or clinicians (Cleophat et al. 2018; Qureshi et al. 2009). Compared with structured genetic interviews, Qureshi et al. found that the tools demonstrated a 75-100% agreement of risk stratification (2009). In Cleophat et al.'s review, the validation methods and results were inconsistent. There was no formal evaluation of clinical utility but similar to our review, Cleophat et al. suggested potential benefits: improved quality of genetic referrals, increased compliance with cancer screening, and no increase in psychological distress (2018).

Finally, both our review and Hilgart et al.'s Cochrane review suggested that familial cancer risk assessment may improve accuracy of patients' risk perception and anxiety,

even though the Cochrane review only included familial breast cancer services delivered by genetic specialists (2012).

Strength of the review & included studies

The strength of this systematic review is the robust search strategy and focused eligibility criteria. Restricting the evidence to the highest level of experimental study design but recognising the paucity of literature in this field, we expanded the inclusion criteria beyond RCT to NRSI. Two independent reviewers conducted the eligibility screen, data extraction and risk of bias assessment. To help interpret the results, we conducted rigorous assessment of the evidence quality using established methods from Cochrane and GRADE (Higgins et al. 2011a; Schünemann et al. 2013; Sterne et al. 2016).

Two of three included studies employed cluster RCT design, which is suitable for studies in primary care where cross contamination of participants in the same primary care practice can dilute the effect of the intervention (Emery et al. 2007; Family Healthware Trial). Included studies also used validated measures for psychological outcomes: in Van Erkelen's study, the impact of familial cancer risk assessment on patient psychological outcomes were measured using STAI and HADS (2017).

Weakness of the review & included studies

Due to the low number of included studies with variable study designs and interventions, a quantitative synthesis was not feasible. The study design requirement of an intervention study and a comparator group increased the review's robustness but limited the number of included studies. Further, risk of bias was high across all studies, hence the results need to be interpreted with caution.

Studies that combined data for patients with and without previous cancer history were excluded. As the aim of the review was to identify the impact of intervention on cancer mortality and morbidity, it was decided that participants with cancer history would not be included. Similarly, studies that combined outcome data for different cancers that could not be disentangled were excluded.

It was difficult to have a true comparator that reflected current usual care. In Emery et al.'s RCT, the lead clinician in both the intervention and control arm received an education session on cancer genetics, although continuing medical education could be considered as part of usual practice (2007). In the Family Healthware trial, the control arm had a lengthy baseline survey, which may have had an intervention effect (Rubinstein et al. 2011a). Finally, studies predominantly included white educated females, limiting the findings' generalisability to the wider population.

Implication for future research

More studies are needed in primary care settings where the majority of health consultations take place (NHS England 2013). Current studies are not generalizable to the wider population; in particular, future studies need better representation from deprived and ethnic minority groups. Future studies should also incorporate robust comparator groups and use validated outcome measures. Current studies often do not state the participants' age range or personal history of cancer in the eligibility criteria, necessitating correspondence with the author. We suggest future studies should also make these inclusion criteria clearer.

Clinical trials with longer follow up will allow for evaluation of clinical impact such as cancer related outcome, but with relatively low prevalence of cancers with inherited

predisposition, this would require studies with large sample sizes. Although classified as lower level of evidence, prospective cohort studies with robust design and longer follow up may provide good quality clinical outcome data.

It has been 30 years since the introduction of familial cancer clinics, and since then there has been great advances in preventive management of familial cancer risk. We still need large well design studies to help us determine if systematic familial cancer risk assessment should be introduced as a routine case-finding approach in primary care.

Supplementary materials

Supplementary materials are available on the journal's website.

Compliance with Ethical Standards

Funding: SL and MP are National Institute for Health Research (NIHR) funded Academic Clinical Fellows.

Conflict of interest: NQ is a member of the NICE Guideline Development Group for familial breast cancer and the advisory board of the Journal of Community Genetics.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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Van Erkelens A, Sie AS, Manders P et al (2017) Online self-test identifies women at high familial breast cancer risk in population-based breast cancer screening without inducing anxiety or distress. Eur J Cancer 78:45-52. https://doi.org/10.1016/j.ejca.2017.03.014

Voils C. (2017) Impact of Family History and Decision Support on High-risk Cancer Screening. ClinicalTrials.gov. https://clinicaltrials.gov/show/NCT02247336 Accessed 10th October 2018

Walker JG, Licqurish S, Chiang PPC, Pirotta M, Emery JD. (2015) Cancer Risk Assessment Tools in Primary Care: A Systematic Review of Randomized Controlled Trials. Ann Fam Med 13(5):480-489. https://doi.org/10.1370/afm.1837

Wang C, Sen A, Plegue M et al (2015) Impact of family history assessment on communication with family members and health care providers: A report from the Family Healthware Impact Trial (FHITr). Prev Med 77:28-34. https://doi.org/10.1016/j.ypmed.2015.04.007

Wang C, Sen A, Ruffin MTt et al (2012) Family history assessment: impact on disease risk perceptions. Am J Prev Med 43(4):392-398. https://doi.org/10.1016/j.amepre.2012.06.013

Wilson BJ, Torrance N, Mollison J et al (2005) Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions. Health Technology Assessment (Winchester, England). 9(3):iii-iv, 1-12

Wilson BJ, Torrance N, Mollison J et al (2006) Cluster randomized trial of a multifaceted primary care decision-support intervention for inherited breast cancer risk. Fam Pract 23(5):537-544. https://doi.org/10.1093/fampra/cml026

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Wu RR, Orlando LA, Himmel TL et al (2013) Patient and primary care provider experience using a family health history collection, risk stratification, and clinical decision support tool: a type 2 hybrid controlled implementation-effectiveness trial. BMC Fam Pract 14:111. https://doi.org/10.1186/1471-2296-14-111

Figure 1. PRISMA flow diagram of study selection.

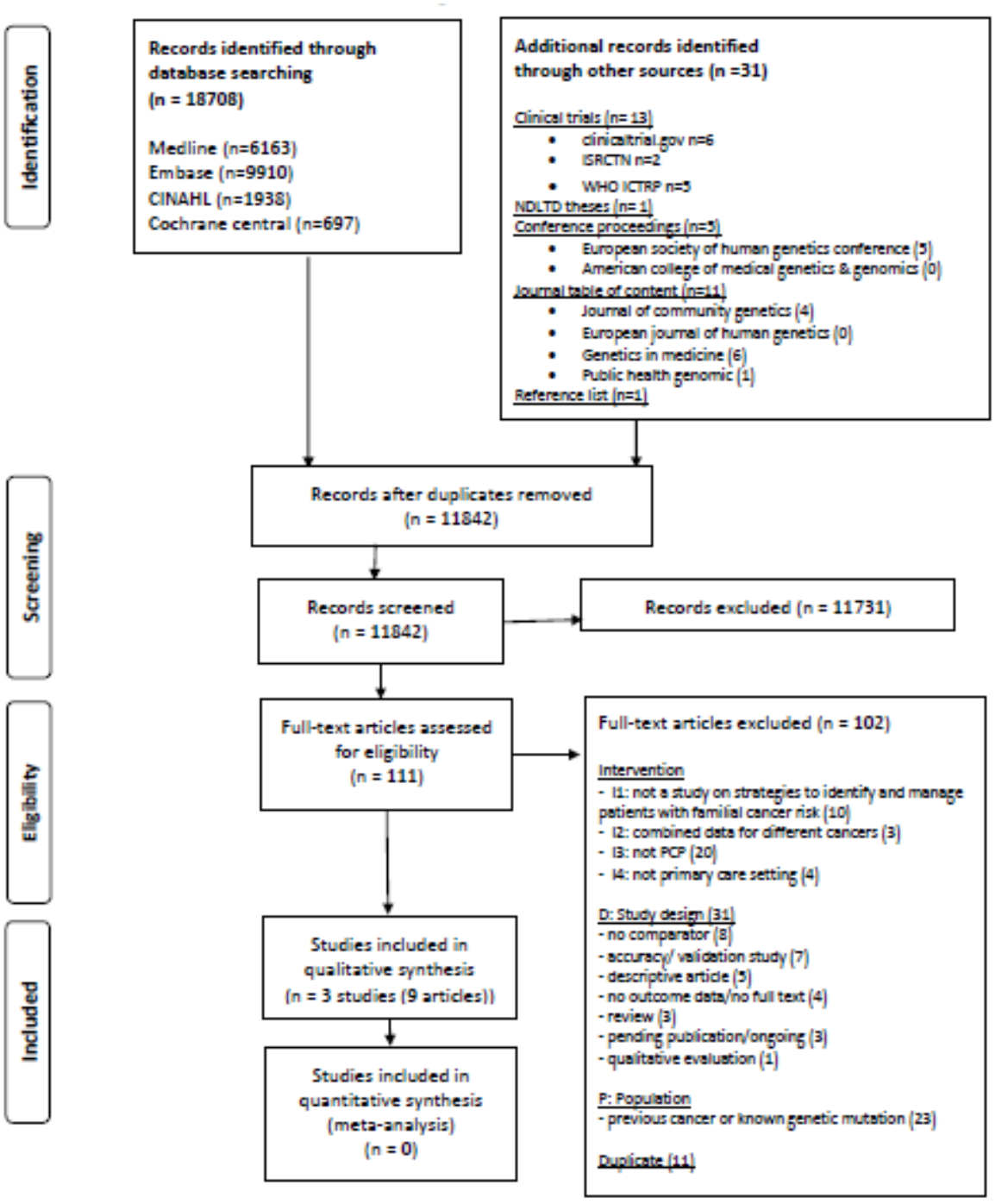


Table 1: Summary description of included studies

Author, year	Study design	Country, setting	Participants	Intervention	Comparator	Outcomes
Emery et al. 2007	Cluster RCT	UK, primary care	Patients expressing concern about cancer family history	Lead clinician attended educational session and given access to software that conducts familial risk assessment to inform genetic referrals.	Lead clinician attended educational session and mailed familial cancer guidelines.	**1. Proportion of GP referrals consistent with guidelines** **2. Proportion of GP referrals assessed to be at increased risk by genetic clinic**
Family Healthware Trial 1. O'Neill et al. 2009 2. Acheson et al. 2010 3. Rubinstein et al. 2011a 4. Rubinstein et al. 2011b 5. Ruffin et al. 2011 6. Wang et al. 2012 7. Wang et al. 2015	Cluster RCT	USA, primary care	Existing patient list or patients with upcoming appointments	Patient received personalised familial risk assessment and prevention messages generated by a software.	Patient received standard prevention messages about screening and healthy lifestyle choices.	**1. Adherence to cancer screening** **2. Cognitive: Patient risk perception**
Van Erkelens et al. 2017	NRSI: uncontrolled before after study	The Netherlands, population BC screening programme	Women attending population BC screening	Patient completed FBC risk assessment and received risk status and advice online.	Same patients two weeks after initial FBC risk assessment.	**Psychological: Patient anxiety & depression (STAI & HADS)**

BC: breast cancer, FBC: familial breast cancer, GP: general practitioner, HADS: Hospital Anxiety Depression Scale, NRSI: non-randomised study of intervention, RCT: randomised controlled trial, STAI: State-Trait Anxiety Inventory

Table 2: GRADE evidence profile

Outcome / cancer	Effect*	Number of participants (studies)	GRADE criteria					Certainty in evidence
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
I. Appropriateness of specialist referral: general practitioners' referral letter (Emery et al. 2007)								
Breast	**Proportions meeting referral guidelines** OR 4.5 (1.6 to 13.1)	45 practices, 167 patients (1 cluster RCT)	Present	Not applicable	Not serious	Absent	Not applicable	⊕⊕◯◯ [a] Low
	Proportions confirmed at increased risk at genetic clinic OR 1.4 (0.6 to 3.5)	45 practices, 111 patients (1 cluster RCT)	Present	Not applicable	Not serious	Present	Not applicable	⊕◯◯◯ [b] Very low
Colorectal	**Proportions meeting referral guidelines** OR 6.5 (0.5 to 83.7)	45 practices, 101 patients (1 cluster RCT)	Present	Not applicable	Not serious	Present	Not applicable	⊕◯◯◯ [c] Very low
	Proportions confirmed at increased risk at genetic clinic OR 0.2 (0.1 to 0.8)	45 practices, 74 patients (1 cluster RCT)	Present	Not applicable	Not serious	Absent	Not applicable	⊕◯◯◯ [d] Very low

[*] Effects are adjusted odds ratio (95% confidence intervals) unless otherwise specified

[a] downgraded by 1 for high risk of bias (allocation concealment, blinding, responder bias), downgraded by 1 as unable to assess inconsistency and publication bias

[b] downgraded by 2 for high risk of bias (allocation concealment, blinding, incomplete outcome (participant non-attendance), responder bias) and imprecision (confidence interval crossing one), downgraded by 1 as unable to assess inconsistency and publication bias

[c] downgraded by 2 for high risk of bias (allocation concealment, blinding, responder bias) and imprecision (wide confidence interval), downgraded by 1 as unable to assess inconsistency and publication bias

[d] downgraded by 2 for high risk of bias (allocation concealment, blinding, incomplete outcome (participant non-attendance), responder bias), downgraded by 1 as unable to assess inconsistency and publication bias

Outcome / cancer	Effect*	Number of participants (studies)	GRADE criteria					Certainty in evidence
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
II. Uptake of preventive strategies: improvement in proportion of patients adherent to risk based screening (Rubinstein et al. 2011a)								
Breast	**Mammography** 9% (intervention) vs 7% (control) improvement, p=0.82	41 practices, 2063 patients (1 cluster RCT)	Present	Not applicable	Absent	Present	Not applicable	⊕◯◯◯ [a] Very low
Colorectal	**Colon cancer screening** 8% vs 7% improvement, p=0.95	41 practices, 2016 patients (1 cluster RCT)	Present	Not applicable	Absent	Present	Not applicable	⊕◯◯◯ [b] Very low

[*] Effects are difference in screening adherence pre- and post-intervention period, p value for comparison between study arms, adjusting for practice clustering, risk, and baseline adherence.

[a, b,] Downgraded by 2 for high risk of bias (randomisation, allocation concealment, blinding, incomplete outcome, selective reporting) and imprecision (no sample size and confidence interval crosses zero); downgraded by 1 as unable to assess inconsistency and publication bias

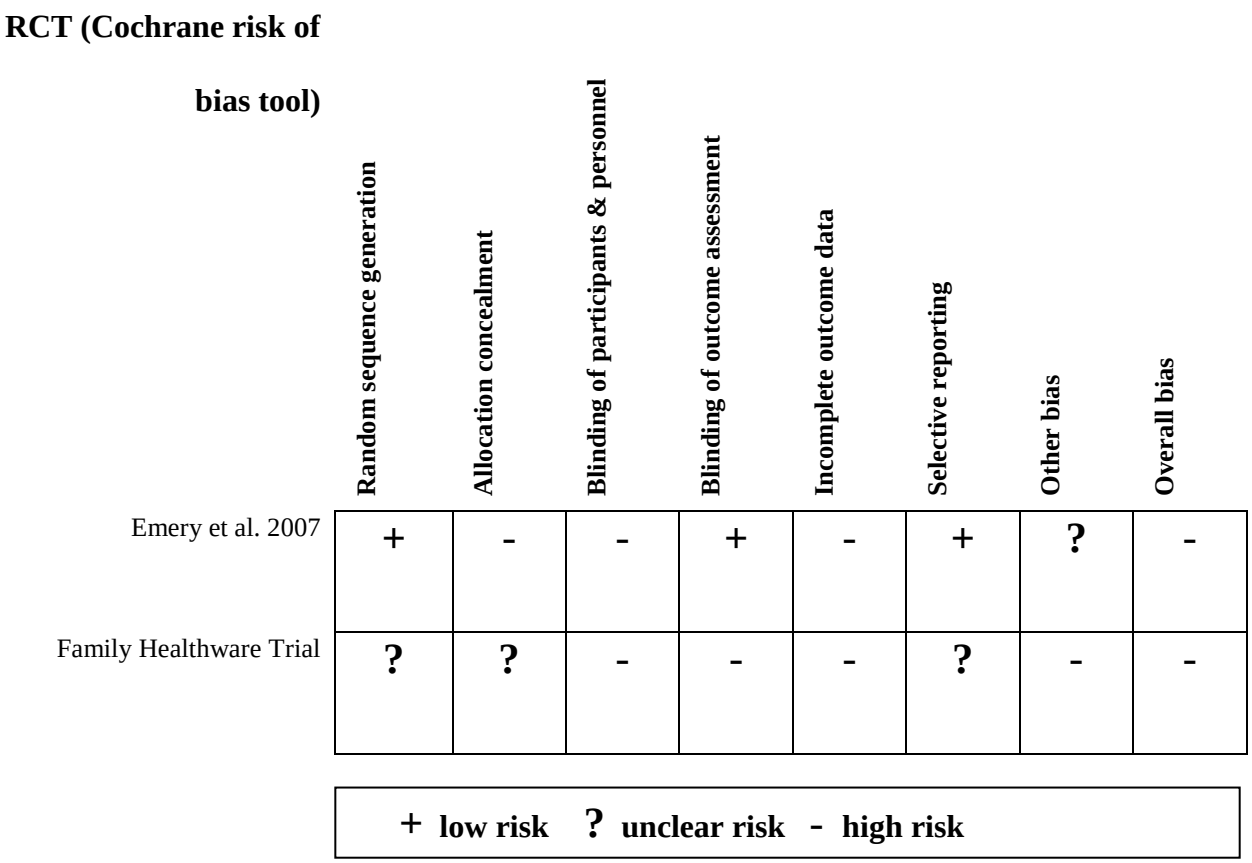
Outcome / cancer	Effect*	Number of participants (studies)	GRADE criteria					Certainty in evidence
			Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	
III. Psychological: patients' anxiety & distress (Van Erkelens et al. 2017)								
Breast	**State anxiety (STAI) immediately after self-test** Increased risk -2 (-6 to 2) Population risk -2 (-2 to -1)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕◯◯◯ [a] Very low
Breast	**State anxiety (STAI) two weeks after self-test** Increased risk 3 (-5 to 10) Population risk -3 (-5 to -2)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕◯◯◯ [b] Very low

Breast	**Trait anxiety (STAI) two weeks after self-test** Increased risk 0 (-3 to 4) Population risk -1 (-2 to -1)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕◯◯◯ [c] Very low
Breast	**Hospital anxiety & depression score (HADS) two weeks after self-test** Increased risk 1 (-3 to 6) Population risk -0 (-1 to 0)	186 patients (1 uncontrolled before after study)	Present	Not applicable	Absent	Present	Not applicable	⊕◯◯◯ [d] Very low

*Effects are mean change from baseline (95% confidence intervals) unless otherwise specified

[a, b, c, d] Downgraded by 2 for critical risk of bias (non-randomised studies of intervention, confounding, missing data) and imprecision (no sample size calculation) , downgraded by 1 as unable to assess inconsistency and publication bias

Table 3: Risk of bias table



NRSI (ROBINS-I risk of bias tool)	**Confounding**	**Participants selection**	**Classification of intervention**	**Deviation from intended interventions**	**Missing data**	**Measurement of outcomes**	**Selection of reported result**	**Overall bias**
Van Erkelens et al. 2017	Critical	Serious	Moderate	Low	Serious	Moderate	Moderate	Critical

Title: Effectiveness of interventions to identify and manage patients with familial cancer risk in primary care: a systematic review

Journal: Journal of Community Genetics

Authors: Siang Ing Lee, Mitesh Patel, Brittany Dutton, Stephen Weng, Jocelyn Luveta, Nadeem Qureshi

Affiliation: Division of Primary Care, School of Medicine, University of Nottingham

Corresponding author: nadeem.qureshi@nottingham.ac.uk

Supplementary material 1: Search strategy

MEDLINE

1	exp Prostatic Neoplasms/
2	exp Breast Neoplasms/
3	exp Ovarian Neoplasms/
4	exp Colorectal Neoplasms/
5	((prostat* or breast* or mammar* or ovar* or colon* or colorect*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or malignan* or adenocarcinoma* or sarcoma*)).mp.
6	Or/1-5
7	exp Genetic Predisposition to Disease/

8	exp Neoplastic Syndromes, Hereditary/
9	(famil* or heredit* or inherit* or gene* or predispos* or susceptib*).mp.
10	exp Genes, BRCA2/ or Genes, BRCA1/
11	exp Tumor Suppressor Protein p53/
12	exp Genetics
13	Or/7-12
14	Exp primary health care/ or exp general practice/ or exp family practice/ or exp physicians, family/ or exp community health services/ or exp ambulatory care/ or exp ambulatory care facilities/ or exp general practitioners/ or exp physicians, primary care/
15	(Primary adj2 care).mp.
16	General practi*.mp.
17	(Family adj2 (practi* or medicine or care or physic*)).mp.
18	communit*.mp.
19	Or/14-18
20	And/6, 13, 19
21	limit 20 to (english language and yr="1980 -Current" and humans)

EMBASE

1	exp prostate tumor/ or exp prostate cancer/
2	exp breast tumor/ or exp breast cancer/
3	exp ovary tumor/ or exp ovary cancer/
4	exp colon cancer/ or exp colon tumor/ or exp rectum tumor/ or exp rectum cancer/ or colorectal tumor/ or colorectal cancer/
5	((prostat* or breast* or mammar* or ovar* or colon* or colorect*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or malignan* or adenocarcinoma* or sarcoma*)).mp.
6	or/1-5
7	exp genetic predisposition/
8	exp hereditary tumor/ or exp cancer genetics/ or exp familial disease/ or exp tumor syndrome/ or exp familial colon polyposis/ or exp "hereditary breast and ovarian cancer syndrome"/ or exp hereditary colorectal cancer/ or exp heredity/
9	exp genetics/
10	(famil* or heredit* or inherit* or gene* or predispos* or susceptib*).mp.
11	exp oncogene/
12	exp primary medical care/ or exp primary health care/

13	exp general practice/ or exp general practitioner/
14	exp family medicine/
15	exp community care/
16	exp ambulatory care/
17	(Primary adj2 care).mp.
18	General practi*.mp.
19	(Family adj2 (practi* or medicine or care or physic*)).mp.
20	communit*.mp.
21	or/7-11
22	or/12-20
23	6 and 21 and 22
24	limit 23 to (human and english language and yr="1980 -Current")

CINAHL

1	(MH "Prostatic Neoplasms+") OR (MH "Breast Neoplasms+") OR (MH "Ovarian Neoplasms+") OR (MH "Colorectal Neoplasms+") OR ""(prostat* or breast* or mammar* or ovar* or colon* or colorect*) N3 (cancer* or neoplasm* or carcinoma* or tumo#r* or malignan* or adenocarcinoma* or sarcoma*)""
2	(MH "Neoplastic Syndromes, Hereditary+") OR ""famil* or heredit* or inherit* or gene* or predispos* or susceptib*"" OR (MH "Genes, BRCA") OR (MH "Genetics, Medical+")
3	(MH "Primary Health Care") OR (MH "Physicians, Family") OR (MH "Family Practice") OR (MH "Ambulatory Care") OR (MH "Community Health Centers+") OR (MH "Ambulatory Care Facilities+") OR ""primary N2 care"" OR ""General practi*"" OR "“(Family N2 (practi* or medicine or care or physic*)”" OR "communit*"
	Limiters - Published Date: 19800101-20171231 Narrow by Language: - english Search modes - Boolean/Phrase

Cochrane CENTRAL

#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	MeSH descriptor: [Breast Neoplasms] explode all trees
#3	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#4	MeSH descriptor: [Colorectal Neoplasms] explode all trees
#5	(prostat* or breast* or mammar* or ovar* or colon* or colorect*) near/3 (cancer* or neoplasm* or carcinoma* or tumo*r* or malignan* or adenocarcinoma* or sarcoma*)
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees
#8	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees
#9	MeSH descriptor: [Genes, BRCA1] explode all trees
#10	MeSH descriptor: [Genes, BRCA2] explode all trees
#11	MeSH descriptor: [Genes, p53] explode all trees
#12	MeSH descriptor: [Genetics] explode all trees
#13	famil* or heredit* or inherit* or gene* or predispos* or susceptib*

#14	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	MeSH descriptor: [Primary Health Care] explode all trees
#16	MeSH descriptor: [Physicians, Primary Care] explode all trees
#17	MeSH descriptor: [General Practice] explode all trees
#18	MeSH descriptor: [General Practitioners] explode all trees
#19	MeSH descriptor: [Physicians, Family] explode all trees
#20	MeSH descriptor: [Ambulatory Care] explode all trees
#21	MeSH descriptor: [Ambulatory Care Facilities] explode all trees
#22	MeSH descriptor: [Community Health Services] explode all trees
#23	"Primary near/2 care"
#24	"General practi*"
#25	Family near/2 (practi* or medicine or care or physic*)
#26	communit*
#27	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28	#6 AND #14 AND #27

U.S. National Institutes of Health (www.clinicaltrials.gov)

Familial Breast Cancer OR hereditary breast cancer OR familial ovarian cancer OR hereditary ovarian cancer OR familial prostate cancer OR hereditary prostate cancer OR familial colorectal cancer OR hereditary colorectal cancer

ISRCTN registry (www.isrctn.com)

Familial breast cancer
Hereditary breast cancer
Familial ovarian cancer
Hereditary ovarian cancer
Familial prostate cancer
Hereditary prostate cancer
Familial colorectal cancer
Hereditary colorectal cancer

WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en)

(prostate cancer OR breast cancer OR ovarian cancer OR colorectal cancer) AND (familial OR hereditary OR inherited OR genetic)

The Networked Digital Library of Theses and Dissertations

"("prostate cancer" OR "breast cancer" OR "ovarian cancer" OR "colorectal cancer") AND ("familial" OR "hereditary" OR "genetic" OR "inherited") AND ("primary care" OR "general practice" OR "general practitioners" OR "family practice" OR "family physicians" OR "community health" OR "ambulatory care")"
Year 1980 -2017, English

Supplementary material 2: List of excluded studies

No	Study reference	Reason for exclusion
1.	Anonymous. UK MoD to conduct cancer screening trial. *Manufacturing Chemist.* 2001;72(11):9	I1: Not a study on strategies to identify and manage patients with familial cancer risk.
2.	Appel SJ, Cleiment RJ. Identifying Women at Risk for Hereditary Breast and Ovarian Cancer Syndrome Utilizing Breast Care Nurse Navigation at Mammography and Imaging Centers. *Journal of National Black Nurses Association.* 2015;26(2):17-26.	I3: Specialist nurse navigator.
3.	Baer HJ, Schneider LI, Colditz GA, et al. Evaluation of a web-based risk assessment tool in the primary care setting. *Journal of General Internal Medicine.* 2012;27:S187.	Duplicate.
4.	Baer HJ, Schneider LI, Colditz GA, et al. Use of a web-based risk appraisal tool for assessing family history and lifestyle factors in primary care. *Journal of General Internal Medicine.* 2013;28(6):817-824.	P: Participants had previous cancer; study outcome not included (increased family history documentation).
5.	Bale PW, Pearce K. The role of primary care physicians in the prevention and management of colorectal cancer. *J Ky Med Assoc.* 2009;107(3):88-92	D: Review article.

6.	Beck S, Breckenridge-Potterf S, Wallace S, Ware J, Asay E, Giles RT. The family High-Risk Program: targeted cancer prevention. *Oncology Nursing Forum.* 1988;15(3):301-306.	I3: Family history questionnaire analysed by the university team, not primary care.
7.	Bellcross CA, Lemke AA, Pape LS, Tess AL, Meisner LT. Evaluation of a breast/ovarian cancer genetics referral screening tool in a mammography population. *Genet Med.* 2009;11(11):783-789.	D: Accuracy study.
8.	Bellcross C. Identification and Referral of Women at Risk for Hereditary Breast/Ovarian Cancer. 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT02786147. Accessed September 24, 2018.	I1: Preselected high-risk participants. Study aim is to identify the most effective means of follow up for women who screened positive on Breast Cancer Genetics Referral Screening Tool. Ongoing trial.
9.	Birt L, Emery JD, Prevost AT, Sutton S, Walter FM. Psychological impact of family history risk assessment in primary care: a mixed methods study. *Fam Pract.* 2014;31(4):409-418.	I2: Combined data for different cancer types.

10.	Biswas S, Atienza P, Chipman J, et al. A two-stage approach to genetic risk assessment in primary care. *Breast Cancer Res Treat.* 2016;155(2):375-383.	D: Accuracy study.
11.	Bondurant KL, Harvey S, Klimberg S, Kadlubar S, Phillips MM. Establishment of a southern breast cancer cohort. *Breast J.* 2011;17(3):281-288.	I1: Not an interventional study on familial risk identification and management.
12.	Bowen DJ, Powers D. Effects of a mail and telephone intervention on breast health behaviors. *Health Education & Behavior.* 2010;37(4):479-489.	I3: No PCP involvement, results not to be given to health provider to avoid risk of insurance discrimination.
13.	Bowman MA, Neale AV, Seehusen DA. Research on clinical decisions made daily in family medicine. *Journal of the American Board of Family Medicine.* 2017;30(3):269-271	I1: Not a study on strategies to identify and manage patients with familial cancer risk. Editor's note.
14.	Brindley C. Proactive familial breast cancer risk assessment in primary care (Phase 2) 2014. Available at: http://www.isrctn.com/ISRCTN16117197. Accessed September 24, 2018.	D: Pending publication.

15.	Brinton JT, Barke LD, Freivogel ME, Jackson S, O'Donnell CI, Glueck DH. Breast Cancer Risk Assessment in 64,659 Women at a Single High-Volume Mammography Clinic. *Academic Radiology.* 2012;19(1):95-99.	P: Included patient with DCIS and LCIS.
16.	Bruner DW, Baffoe-Bonnie A, Miller S, et al. Prostate cancer risk assessment program. A model for the early detection of prostate cancer. *Oncology (Williston Park).* 1999;13(3):325-334; discussion 337-329, 343-324 pas.	I3: Specialist provider.
17.	Burke C, Leach B, Dai J, et al. Community uptake of an online CRC risk assessment. *American Journal of Gastroenterology.* 2010;105:S549.	Duplicate.
18.	Burke CA, Leach B, Dai J, et al. The community uptake of an online CRC risk assessment and its utility to assess for a potential hereditary colon cancer syndrome. *Hereditary Cancer in Clinical Practice.* 2011;9:5-6.	I3: Assessment self-administered by patients, unclear who acted on results. Multispecialty academic medical centre. Patients with previous cancer. No reply from author.
19.	Byers T, Lynch HT, Thun M. Biomarkers of cancer risk: at a turning point? *Patient Care for the Nurse Practitioner.* 2002;5(8):9p-9p.	D: Review article.

20.	Campacci N, Ramadan L, Caron TB, et al. Identification of at-risk families for hereditary breast cancer through a Brazilian cancer prevention network in a population. *Current Oncology*. 2012;19 (2):e110.	I3: Specialist provider in cancer hospital.
21.	Chorley W, Dutton B, Brindley C, Robles L, Qureshi N. From national guideline recommendations to familial cancer risk assessment decision support in primary care: UK experience Paper presented at: European Human Genetics Conference. Glasgow. June, 2015.	D: No comparator, abstract, duplicate.
22.	Clark R. Implementation of a Risk Assessment Process in a Primary Clinic to Identify Women at High Risk for Developing Breast Cancer Based on Family History [dissertation]. Ann Arbor: University of Louisiana at Lafayette, 2016	P: Unclear how many of those at high risk had previous cancer and whether patients with known genetic mutation were included, no comparator, no reply from author.
23.	Cohen SA, Nixon DM. A collaborative approach to cancer risk assessment services using genetic counselor extenders in a multi-system community hospital. *Breast Cancer Research and Treatment.* 2016;159(3):527-534.	I3: Trained nurse navigators as genetic counsellor extenders, results reviewed by genetic counsellors.
24.	Colombet I, Xu Y, Jaulent MC, Desages D, Degoulet P, Chatellier G. A generic computerized method for estimate of familial risks. *Proceedings / AMIA* 2002;Annual Symposium.:175-179.	D: Qualitative evaluation of a programme using case scenarios.

25.	Coulson AS, Glasspool DW, Fox J, Emery J. RAGs: A novel approach to computerized genetic risk assessment and decision support from pedigrees. *Methods of Information in Medicine.* 2001;40(4):315-322.	D: Described the features of the risk assessment tool, no outcome data.
26.	Destounis S, Arieno A, Morgan R. Implementation of a risk assessment program in a breast-imaging community practice. *Breast Cancer.* 2016;23(2):273-278.	P: Participants had previous cancer, no comparator.
27.	DiSario JA, Luba DG, Rock C, et al. A prospective evaluation of the feasibility of process engineering intervention on the screening and testing of Lynch syndrome in individuals with a personal and/or family history of Lynch-associated cancers. *Gastroenterology.* 2014;1):S-729.	I4: Community gastroenterology practice.
28.	Eisenbraun A, Wenstrup R, Hellerstedt B, et al. Hereditary breast and ovarian cancer testing: Integration and outcomes within community oncology practices. *Community Oncology.* 2010;7(2):75-81.	I4: Cancer clinic.
29.	Emery J. The GRAIDS Trial: the development and evaluation of computer decision support for cancer genetic risk assessment in primary care. *Annals of Human Biology.* 2005;32(2):218-227.	D: Described a risk assessment tool, not an interventional study.

30.	Emery J, Pirotta M, Walker J, et al. Trialling a colorectal cancer risk tool within general practice; NHMRC "centre for research excellence for reducing the burden of colorectal cancer by optimising screening". *Asia-Pacific Journal of Clinical Oncology.* 2014;10:203-204.	D: Discussed the plan of a trial, not a trial protocol.
31.	Fehniger J, Livaudais-Toman J, Karliner L, et al. Perceived versus objective breast cancer risk in diverse women. *Journal of Women's Health.* 2014;23(5):420-427.	P: May have participants with previous ovarian cancer (correspondence with author). Overall risk of breast cancer.
32.	Goel MS. Breast cancer risk assessment in a primary care, federally qualified community health center population. *Journal of General Internal Medicine.* 2017;32 (2 Supplement 1):S131.	D: No comparator, abstract, full text in progress.
33.	Haas J. Randomized trial of a personalized multi-condition risk assessment in primary care. *International Journal for Quality in Health Care.* 2016;28:42-43.	P: Participants had previous colorectal and breast cancer.
34.	Hoskins KF, Zwaagstra A, Ranz M. Validation of a tool for identifying women at high risk for hereditary breast cancer in population-based screening. *Cancer.* 2006;107(8):1769-1776.	D: Accuracy study.

35.	House W, Sharp D, Sheridan E. Identifying and screening patients at high risk of colorectal cancer in general practice. *J Med Screen.* 1999;6(4):205-208.	P: No separate data for patients with and without cancer (correspondence with author), no comparator.
36.	Howell A, Astley S, Warwick J, et al. Prevention of breast cancer in the context of a national breast screening programme. *Journal of Internal Medicine.* 2012;271(4):321-330.	D: Review article.
37.	Jacobs C, Rawson R, Campion C, et al. Providing a community-based cancer risk assessment service for a socially and ethnically diverse population. *Familial Cancer.* 2007;6(2):189-195.	I3: Specialist nurse.
38.	Joseph G, Kaplan C, Luce J, et al. Efficient identification and referral of low-income women at high risk for hereditary breast cancer: a practice-based approach. *Public Health Genomics.* 2012;15(3-4):172-180.	P: Participants had previous cancer. Evaluating methods to follow up high risk women.
39.	Kadison P, Pelletier EM, Mounib EL, Oppedisano P, Poteat HT. Improved screening for breast cancer associated with a telephone-based risk assessment. *Preventive Medicine.* 1998;27(3):493-501.	P: Participants had previous cancer. Evaluated impact of intervention on screening behaviour for women of all risk, unable to ascertain effect on those with increased familial risk.

40.	Kaplan CP, Lopez M, Tice J, et al. The gap between perceptions of risk and actual risk for breast cancer. *Cancer Research Conference: 35th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Publication:*. 2012;72(24 SUPPL. 3).	Duplicate.
41.	Kaplan CP, Livaudais-Toman J, Gregorich S, et al. Breastcare: A primary care clinic-based RCT to increase breast cancer knowledge and discussion of risk and lifestyle behaviors. *Journal of General Internal Medicine.* 2013;28:S36.	Duplicate.
42.	Kaplan CP, Livaudais-Toman J, Tice JA, et al. A randomized, controlled trial to increase discussion of breast cancer in primary care. *Cancer Epidemiol Biomarkers Prev.* 2014;23(7):1245-1253.	P: May have participants with previous ovarian cancer (correspondence with author). Overall risk of breast cancer.
43.	Kohut K, D'Mello L, Bancroft EK, et al. Implications for cancer genetics practice of pro-actively assessing family history in a General Practice cohort in North West London. *Familial Cancer.* 2012;11(1):107-113.	I3: Questionnaire reviewed by genetic counsellor.

44.	Kulkarni A, Kenney A, Tripathi V, et al. Technological innovation in hereditary cancer risk assessment. Paper presented at: European Human Genetics Conference. Barcelona, May, 2016.	D: No outcome data.
45.	Langer L, Clark L, Gress J, et al. A Structured genetic risk evaluation and testing program in the community oncology practice increases identification of individuals at risk for BRCA Mutations. *Cancer Research Conference: 35th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Publication:*. 2012;72(24 SUPPL. 3).	I4: Community oncology practice.
46.	Leggatt V, Mackay J, Yates JR. Evaluation of questionnaire on cancer family history in identifying patients at increased genetic risk in general practice. *BMJ.* 1999;319(7212):757-758.	D: No comparator.
47.	Leggatt V, Mackay J, Marteau TM, Yates JR. The psychological impact of a cancer family history questionnaire completed in general practice. *Journal of Medical Genetics.* 2000;37(6):470-472.	I2: Combined data for breast and colorectal cancer.

48.	Li X, McGuinness JE, Vanegas A, et al. Identifying women at high-risk for breast cancer using data from the electronic health record compared to self-report. *Journal of Clinical Oncology Conference.* 2017;35(15 Supplement 1).	P: Included participants with LCIS.
49.	Lieberman S, Tomer A, Ben-Chetrit A, et al. From personal genetic counseling to public health screening: The BRCA Opportunity Paper presented at: European Human Genetics Conference; June, 2013; Paris.	I3: Genetic counsellor reviewed family history questionnaires, genetic testing for all participants.
50.	Livaudais-Toman J, Karliner L, Tice J, et al. Impact of a primary care based intervention on breast cancer knowledge, risk perception and concern: a randomized, controlled trial. *Breast (edinburgh, scotland).* 2015;24(6):758-766.	P: May have participants with previous ovarian cancer (correspondence with author). Overall risk of breast cancer.
51.	Lowry H, Dekhne N, Fend D, Lerman R, Gregory N, Boura J. Multidisciplinary high-risk program: A community hospital's experience. *Journal of Clinical Oncology Conference: ASCO Annual Meeting.* 2011;29(15 SUPPL. 1).	Duplicate.
52.	Mackay J, Schulz P, Rubinelli S, Pithers A. Online patient education and risk assessment: project OPERA from Cancerbackup. Putting inherited breast cancer risk information into context using argumentation theory. *Patient Educ Couns.* 2007;67(3):261-266.	D: Explained the theory behind the programme, not an interventional study.

53.	MacSweeney MA, Roorda H, Lippert R, et al. Development and implementation of a breast cancer risk identification and reduction program in a large health care system. *Cancer Research Conference: 37th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Publication:*. 2015;75(9 SUPPL. 1).	D: No comparator, abstract, no reply from author.
54.	Mays D, Sharff ME, DeMarco TA, et al. Outcomes of a systems-level intervention offering breast cancer risk assessments to low-income underserved women. *Familial Cancer.* 2012;11(3):493-502.	I3: Eligible patient records reviewed by medical oncologist, community based breast health centre, no comparator.
55.	McDonnell C, Seidenwurm D, McDonnell D, Dutton A, Bobolis K. Initial experience with tablet computer-based self-administered historical screening for hereditary cancers in conjunction with imaging. *American Journal of Roentgenology.* 2011;196 (5 SUPPL.):A92.	P: Not stated if participants with previous cancer or known genetic mutation were excluded, no comparator.
56.	Murthy VS, Garza MA, Almario DA, et al. Using a family history intervention to improve cancer risk perception in a black community. *Journal of Genetic Counseling.* 2011;20(6):639-649.	I3: Implemented by genetic students.

57.	Naicker S, Meiser B, Goodwin A, et al. A pilot study to evaluate the utility of an online familial risk tool to screen for colorectal cancer. *Asia-Pacific Journal of Clinical Oncology.* 2011;7:127.	Duplicate.
58.	Naicker S, Meiser B, Goodwin A, et al. Which test is best? - A RCT to evaluate family history as a triage tool in screening for colorectal cancer. *Asia-Pacific Journal of Clinical Oncology.* 2012;8:264.	Duplicate.
59.	Naicker S, Meiser B, Goodwin A, et al. Which tests is best? A randomised controlled trial to evaluate the use of familial phenotype to risk appropriately screen for colorectal cancer in the general population. *Psycho-Oncology.* 2013;22:27.	D: Pending publication (author correspondence).
60.	Orlando LA, Hauser ER, Christianson C, et al. What's the impact? Clinical validity and utility of metree, An electronic family history collection and decision support tool for primary care. *Journal of General Internal Medicine.* 2011;26:S35-S36.	D: Accuracy study.
61.	Orlando LA, Hauser ER, Christianson C, et al. Protocol for implementation of family health history collection and decision support into primary care using a computerized family health history system. *BMC Health Serv Res.* 2011;11:264.	P: May include participants with previous cancer, unable to provide data (author correspondence).

62.	Orlando LA, Henrich VC, Hauser ER, Wilson C, Ginsburg GS. Genomedical Connection. The genomic medicine model: an integrated approach to implementation of family health history in primary care. *Per Med*. 2013;10(3):295-306.	P: May include participants with previous cancer, unable to provide data (author correspondence).
63.	Orlando LA, Wu RR, Beadles C, et al. Implementing family health history risk stratification in primary care: impact of guideline criteria on populations and resource demand. *American Journal of Medical Genetics Part C, Seminars in Medical Genetics.* 2014;166C(1):24-33.	D: No comparator.
64.	Orlando LA, Wu R, McCarty C, Dimmock D, Ginsburg GS. From guideline recommendations to familial cancer risk assessment decision support in primary care: US Experience Paper presented at: European Human Genetics Conference. Glasgow. June, 2015.	D: Accuracy study of different guidelines.
65.	Orlando LA, Wu RR, Myers RA, et al. Clinical utility of a Web-enabled risk-assessment and clinical decision support program. *Genet Med.* 2016;18(10):1020-1028.	P: May include participants with previous cancer, unable to provide data (author correspondence).
66.	Owens WL, Gallagher TJ, Kincheloe MJ, Ruetten VL. Implementation in a large health system of a program to identify women at high risk for breast cancer. *Journal of Oncology Practice.* 2011;7(2):85-88.	D: No comparator.

67.	Ozanne EM, Loberg A, Hughes S, et al. Identification and management of women at high risk for hereditary breast/ovarian cancer syndrome. *Breast J.* 2009;15(2):155-162.	I4: Breast care centre, no comparator.
68.	Ozanne E, Omer Z, Carlson K. Automated breast cancer risk assessment: Identifying high risk women in the primary care setting. *Cancer Research Conference: 34th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Publication.* 2011;71(24 SUPPL. 3).	D: Abstract only, no full text (author correspondence).
69.	Ozanne EM, Crawford B, Petruse A, et al. Risk assessment and personalized decision support: the university of california athena breast health network. *Cancer Research Conference: 35th Annual CTRC AACR San Antonio Breast Cancer Symposium San Antonio, TX United States Conference Publication:*. 2012;72(24 SUPPL. 3).	D: Described recruitment, abstract only, no full text (author correspondence).
70.	Paris NM, Gabram-Mendola SGA, Kerber AS, et al. Hereditary breast and ovarian cancer: Risk assessment in minority women and provider knowledge gaps. *Journal of Community and Supportive Oncology.* 2016;14(6):261-267	D: No comparator.
71.	Pieper C, Kolankowska I, Jockel KH. Does a screening questionnaire for familial and hereditary colorectal cancer risk work in a health insurance population? *European Journal of Cancer Care.* 2012;21(6):758-765.	I3: Not PCP, no comparator.

72.	Rafi I, Chowdhury S, Chan T, Jubber I, Tahir M, de Lusignan S. Improving the management of people with a family history of breast cancer in primary care: before and after study of audit-based education. *BMC Family Practice.* 2013;14:105.	I1: Audit on whether low risk women were correctly advised and flagged.
73.	Resta R, Drescher CW, Beatty D, et al. Systematic identification of high risk women for genetic counseling and surgical prevention of ovarian cancer. *Clinical Cancer Research Conference: 10th Biennial Ovarian Cancer Research Symposium United States.* 2015;21(16 Supplement 1).	I1: Evaluated the effect of genetic referral, not PCP.
74.	Rothenberger DA, Dalberg DL, Leininger A. Minnesota Colorectal Cancer Initiative: successful development and implementation of a community-based colorectal cancer registry. *Diseases of the Colon & Rectum.* 2004;47(10):1571-1577.	I3: Genetic counsellor reviewed the enrolment form and assessed risk.
75.	Sariego J, Losa K, Fitzpatrick L. Implementation of a community-based screening program for women at high risk for breast cancer. *Annals of Surgical Oncology.* 2017;24 (2 Supplement 1):118-120.	I3: Community breast care programme led by breast surgeon.
76.	Scheuner MT, Hamilton AB, Peredo J, et al. A cancer genetics toolkit improves access to genetic services through documentation and use of the family history by primary-care clinicians. *Genet Med.* 2014;16(1):60-69.	I2: Combined data for the different cancers. Documentation in medical

		records for the different cancer is not an outcome of interest.
77.	Shah C, Berry S, Dekhne N, Lanni T, Lowry H, Vicini F. Implementation and outcomes of a multidisciplinary high-risk breast cancer program: the William Beaumont Hospital experience. *Clinical Breast Cancer.* 2012;12(3):215-218.	P: Included participants with LCIS.
78.	Skinner CS, Rawl SM, Moser BK, et al. Impact of the Cancer Risk Intake System on patient-clinician discussions of tamoxifen, genetic counseling, and colonoscopy. *Journal of General Internal Medicine.* 2005;20(4):360-365.	P: Included male participants with personal history of breast or colon cancer.
79.	Skinner CS, Halm EA, Bishop WP, et al. Impact of Risk Assessment and Tailored versus Nontailored Risk Information on Colorectal Cancer Testing in Primary Care: A Randomized Controlled Trial. *Cancer Epidemiol Biomarkers Prev.* 2015;24(10):1523-1530.	I1: Evaluated intervention's impact on screening uptake of patients of all risk, unable to ascertain impact on patients with familial cancer risk.
80.	Skinner CS, Gupta S, Bishop WP, et al. Tailored information increases patient/physician discussion of colon cancer risk and testing: The Cancer Risk Intake System trial. *Preventive Medicine Reports.* 2016;4:6-10.	I1: Evaluated intervention's impact on patients of all risk, unable to

		ascertain impact on patients with familial cancer risk.
81.	Skinner CS, Ahn C, Halm EA, et al. Recommendation of colorectal cancer testing among primary care patients younger than 50 with elevated risk. *Preventive Medicine.* 2017;102:20-23.	D: No comparator.
82.	Smith FA, Rozelle-Trosper M, Sterling M, et al. Hereditary cancer risk assessment: Establishing a comprehensive safety net in a large multispecialty group. *Annals of Surgical Oncology.* 2014;21:112.	I3: Nurses from multispecialty clinics.
83.	Stewart SL, Kaplan CP, Lee R, et al. Validation of an Efficient Screening Tool to Identify Low-Income Women at High Risk for Hereditary Breast Cancer. *Public Health Genomics.* 2016;19(6):342-351.	D: Validation study.
84.	SuÁRez-MejÍAs C, MartÍNez-GarcÍA A, MartÍNez-Maestre MÁ, Silvan-Alfaro JM, Moreno Conde J, Parra-CalderÓN CL. Learning Healthcare System for the Prescription of Genetic Testing in the Gynecological Cancer Risk..."Informatics for Health," Manchester, UK, April 2017. *Studies in Health Technology & Informatics.* 2017;235:96-100.	D: No outcome data.

85.	Sweet K, Sturm AC, Rettig A, McElroy J, Agnese D. Clinically relevant lessons from Family HealthLink: a cancer and coronary heart disease familial risk assessment tool. *Genet Med.* 2015;17(6):493-500.	I3: No PCP involvement.
86.	Snyder C, Crihfield PE. Performing Breast Cancer Risk Assessments in a Community Setting. *Clinical Journal of Oncology Nursing.* 2011;15(4):361-364.	P: Not stated whether excluded participants with previous cancer or known genetic mutation, no comparator, no reply from author.
87.	Tozer D, Lugton C. Cancer genetics in rural primary care: a pilot nurse-led service using a new mobile IT system. *Familial Cancer.* 2007;6(2):221-229.	I3: Specialist nurse.
88.	Traxler LB, Martin ML, Kerber AS, et al. Implementing a screening tool for identifying patients at risk for breast and ovarian cancer: A statewide initiative. *Annals of Surgical Oncology.* 2014;21:118	Duplicate.
89.	Trevena L. A Randomised trial of consumer-led familial cancer risk tool & GP triage on risk-appropriate colorectal cancer screening. 2011. Available at: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12611000534987. Accessed September 24, 2018.	Duplicate.

90.	Vieira DKR, Attianezi M, Esposito AC, et al. Identification of familial clustering for cancer through the family health strategy program in the municipality of Angra dos Reis, Rio de Janeiro, Brazil. *Journal of Community Genetics.* 2014;6(1):9-16.	I1: Surveillance in the surrounding of a nuclear plant area for familial cancer clustering.
91.	Voils C. Impact of Family History and Decision Support on High-risk Cancer Screening. ClinicalTrials.gov; 2017. Available at: https://clinicaltrials.gov/show/NCT02247336. Accessed September 24, 2018.	D: Ongoing study.
92.	Walter FM, Prevost AT, Birt L, et al. Development and evaluation of a brief self-completed family history screening tool for common chronic disease prevention in primary care. *British Journal of General Practice.* 2013;63(611):e393-400.	D: Accuracy study.
93.	Wharton HC. Family cancer history and pedigrees as a public health intervention for promoting health and preventing prostate cancer in African-Americans [dissertation]. Clemson University, 2012	P: Included participants with personal prostate cancer.
94.	Wiesman C, Rose E, Grant A, Zimilover A, Klugman S, Schreiber-Agus N. Experiences from a pilot program bringing BRCA1/2 genetic screening to theUS Ashkenazi Jewish population. *Genet Med.* 2017;19(5):529-536.	I3: Genetic counsellor reviewed family history.

95.	Williams RR, Hunt SC, Barlow GK, et al. Health family trees: a tool for finding and helping young family members of coronary and cancer prone pedigrees in Texas and Utah. *Am J Public Health.* 1988;78(10):1283-1286.	I3: Results analysed at genetic research clinic.
96.	Wilson BJ, Torrance N, Mollison J, et al. Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions. *Health Technology Assessment (Winchester, England).* 2005;9(3):iii-iv, 1-12	P: Included participants with previous breast cancer and other cancer.
97.	Wilson BJ, Torrance N, Mollison J, et al. Cluster randomized trial of a multifaceted primary care decision-support intervention for inherited breast cancer risk. *Fam Pract.* 2006;23(5):537-544.	P: Included participants with previous breast cancer and other cancer.
98.	Wu RR, Himmel T, Powell K, et al. Usability of a family health history and clinical decision support tool for patients and primary care providers. *Journal of General Internal Medicine.* 2013;28:S233.	Duplicate.
99.	Wu RR, Orlando LA, Himmel TL, et al. Patient and primary care provider experience using a family health history collection, risk stratification, and clinical decision support tool: a type 2 hybrid controlled implementation-effectiveness trial. *BMC Family Practice.* 2013;14:111.	P: May include patients with personal history of cancer, unable to provide data (author correspondence).

100.	Wu RR, Himmel T, Buchanan A, et al. Impact of a family history collection tool, MeTree©, in identifying individuals at high-risk for cancer and thrombosis. *Journal of General Internal Medicine.* 2013;28:S101.	Duplicate.
101.	Yoon PW, Scheuner MT, Jorgensen C, Khoury MJ. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. *Preventing Chronic Disease.* 2009;6(1):A33.	D: Describes the development of the Family Healthware Tool, no outcome data.
102.	Zazove P, Plegue MA, Uhlmann WR, Ruffin MTt. Prompting Primary Care Providers about Increased Patient Risk As a Result of Family History: Does It Work? *J Am Board Fam Med.* 2015;28(3):334-342.	I1: Studied the effect of electronic prompts on PCP's record keeping for family history.

DCIS: ductal carcinoma in situ, LCIS: lobular carcinoma in situ, PCP: primary care provider

NB: please see PRISMA flowchart for the categories of reasons of exclusion.

Supplementary material 3: Outcome table

<table>
<tr><th>Outcomes</th><th>Study ID</th><th>Results</th></tr>
<tr><td colspan="3">Appropriateness of specialist referrals</td></tr>
<tr><td>Included studies</td><td>Emery et al. 2007</td><td>
Proportions of GP referral letters meeting guidelines
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>OR (95% CI)</th></tr>
<tr><td>Breast</td><td>93% (99/107)</td><td>73% (44/60)</td><td>4.5 (1.6 to 13.1)</td></tr>
<tr><td>Bowel</td><td>99% (15/76)</td><td>92% (23/25)</td><td>6.5 (0.5 to 83.7)</td></tr>
<tr><td>Combined</td><td>95% (174/183)</td><td>79% (67/85)</td><td>5.2 (1.7 to 15.8)
P=0.006</td></tr>
</table>
Proportions of GP referrals confirmed at increased risk at genetic clinic
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>OR (95% CI)</th></tr>
<tr><td>Breast</td><td>77% (60/78)</td><td>70% (23/33)</td><td>1.4 (0.6 to 3.5)</td></tr>
<tr><td>Bowel</td><td>56% (30/54)</td><td>85% (17/20)</td><td>0.2 (0.1 to 0.8)</td></tr>
<tr><td>Combined</td><td>68% (90/132)</td><td>75% (40/53)</td><td>0.7 (0.3 to 1.5)
P=0.35</td></tr>
</table>
NB: Odds ratio for intervention vs. control allowing for cluster randomised design.
</td></tr>
</table>

<table>
<tr>
<td>Studies excluded for having participants with personal history of cancer</td>
<td>Wilson et al. 2005; Wilson et al. 2006</td>
<td>
Proportion of GP referral letters categorised as increased risk
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>RR (95% CI)</th><th>P value[a]</th></tr>
<tr><td>Pre intervention</td><td>55% (53/96)</td><td>65% (24/37)</td><td>0.85 (0.63 to 1.15)</td><td>0.31 (0.31)[b]</td></tr>
<tr><td>Post intervention</td><td>65% (66/102)</td><td>60% (22/37)</td><td>1.09 (0.80 to 1.47)</td><td>0.57</td></tr>
</table>
Proportion of referred patients confirmed at increased risk at genetic clinic
<table>
<tr><th></th><th>Intervention</th><th>Control</th><th>RR (95% CI)</th><th>P value[b]</th></tr>
<tr><td>Pre intervention</td><td>46% (40/88)</td><td>65% (22/34)</td><td>0.70 (0.50 to 0.99)</td><td>0.06</td></tr>
<tr><td>Post intervention</td><td>58% (49/85)</td><td>48% (14/29)</td><td>1.18 (0.88 to 1.37)</td><td>0.38</td></tr>
</table>
[a] Pearson x^2
[b] Pearson x^2 adjusted for clustering within practices
</td>
</tr>
</table>

Uptake of preventive strategies

Included studies — Family healthware trial

Proportion of patients adherent to cancer screening (Rubinstein et al. 2011a)

Reported in text only:

	Intervention (%)		**Control (%)**		P value[a]
	Baseline	6 months	Baseline	6 months	
Mammography	73	82	78	85	0.82
Colorectal cancer screening	76	84	77	84	0.95

[a]comparison between arms, adjusted for clustering, risk, baseline adherence

Proportion of non-adherent patients becoming adherent to cancer screening at six months (Rubinstein et al. 2011a)

	Intervention %improved	**Control %improved**	**OR (95% CI)[a]**	**P value**
Breast cancer risk				
Strong	60% (27/45)	65% (17/26)	0.8 (0.3 to 2.2)	0.65
Moderate	63% (22/35)	59% (10/17)	0.7 (0.4 to 1.4)	0.28
Weak	58% (157/272)	64% (77/120)	1.0 (0.6 to 1.6)	0.92
Overall[b]	59% (206/352)	64% (104/163)	0.9 (0.6 to 1.5)	0.82
Colorectal cancer risk				

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>Strong</td><td>36% (5/14)</td><td>21% (3/14)</td><td>1.9 (0.5 to 7.2)</td><td>0.33</td></tr>
<tr><td>Moderate</td><td>16% (9/55)</td><td>18% (6/33)</td><td>0.9 (0.3 to 3.1)</td><td>0.86</td></tr>
<tr><td>Weak</td><td>40% (90/222)</td><td>43% (58/134)</td><td>0.9 (0.6 to 1.6)</td><td>0.77</td></tr>
<tr><td>Overall[b]</td><td>36% (104/291)</td><td>37% (67/181)</td><td>0.9 (0.6 to 1.4)</td><td>0.77</td></tr>
</table>
Breast cancer – mammography
Colon cancer – faecal occult blood, sigmoidoscopy, or colonoscopy
[a]Unadjusted OR
[b]Adjusted for risk

Proportion of women with ovaries having CA-125 blood test and transvaginal ultrasound during the six month follow up (Rubinstein et al. 2011a)

Reported in text only: CA-125 test 47 (2%), transvaginal ultrasound 100 (5%), no measurable difference between the study arms (p>0.09) (separate data for study arms or risk level not provided)
</td></tr>
<tr><td>Studies excluded for having participants with personal history of cancer</td><td>MeTree</td><td>
Proportions of patients receiving risk-management strategy before and after using MeTree (Orlando et al. 2016)
<table>
<tr><th></th><th colspan="2">Increased risk (received appropriate management)</th><th colspan="2">Not at increased risk (received management inappropriately)</th></tr>
<tr><th>Risk-management strategy</th><th>Before MeTree</th><th>After MeTree</th><th>Before MeTree</th><th>After MeTree</th></tr>
<tr><td>Breast cancer: Magnetic Resonance Imaging (MRI)</td><td>25% (1/4)</td><td>75% (3/4)</td><td>2% (5/280)</td><td>0.4% (1/280)</td></tr>
</table>
</td></tr>
</table>

Breast cancer: chemoprevention	0% (0/26)	0% (0/26)	0% (0/258)	0% (0/258)
Ovarian cancer: referral to gynaecology	0% (0/2)	50% (1/2)	4% (12/282)	3% (9/282)

NB: Women only. Colon cancer risk recommendations were excluded from this table because the assessment could only be accurately completed in those < 50 years of age.

Control arm's breast cancer screening rates suggest temporal changes did not result in increased breast cancer screening in the intervention arm (Orlando et al. 2016)

Reported in text only:

Control screening rate	**Before**	**After**	**P value**
Breast MRI	0%	1.8%	0.32
Mammography	62.5%	48.2%	0.13

Screening rates after study date	**Intervention**	**Control**	**P value**
Breast MRI	0.74%	1.8%	0.371
Mammography	76.0%	48.2%	0.003

<table>
<tr><th colspan="3">Cognitive effect: Patients' risk perception</th></tr>
<tr><td>Included studies</td><td>Family healthware trial</td><td>Proportion of patient with risk perception consistent with risk status by Family Healthware at baseline (Wang et al. 2012)

<table>
<tr><th></th><th>Low familial risk</th><th>High familial risk</th></tr>
<tr><td colspan="3">Breast cancer</td></tr>
<tr><td>Intervention</td><td>92% (1152/1250)</td><td>52% (212/405)</td></tr>
<tr><td>Control</td><td>92% (602/655)</td><td>49% (96/194)</td></tr>
<tr><td colspan="3">Ovarian cancer</td></tr>
<tr><td>Intervention</td><td>96% (1324/1382)</td><td>30% (42/140)</td></tr>
<tr><td>Control</td><td>97% (685/707)</td><td>27% (20/73)</td></tr>
<tr><td colspan="3">Colon cancer</td></tr>
<tr><td>Intervention</td><td>94% (1893/2015)</td><td>46% (146 /315)</td></tr>
<tr><td>Control</td><td>95% (1015/1069)</td><td>42% (78/186)</td></tr>
</table>

Proportion of under-estimator shifting to high perceived risk (consistent with risk status) and logistic regression model predicting this shift at six months follow up (Wang et al. 2012)
<table>
<tr><th>Cancer</th><th>N</th><th>Intervention</th><th>Control</th><th>OR (95% CI)[a]</th></tr>
<tr><td>Breast</td><td>276</td><td>18%</td><td>14%</td><td>1.48 (0.61 to 3.58)</td></tr>
</table>
</td></tr>
</table>

		Ovarian	140	8%	13%	0.52 (0.10 to 2.59)
		Colon	258	17%	10%	1.89 (0.99 to 3.59)[b]

[a] Control arm as reference, models adjusted for practice clustering and potential site difference
[b] Statistically significant (p=0.05)

Psychological effect: Patients' anxiety & depression

Included studies — Van Erkelens et al. 2017

Anxiety & depression at baseline, immediately after and two weeks after familial breast cancer risk self-assessment

Outcome	N	Baseline mean (SD)	After mean (SD)	Mean change from baseline (95% CI)	P value
Immediately after					
State anxiety (STAI 20-80)[a]					
Increased risk	15	36 (12)	34 (13)	-2 (-6 to 2)	0.357
Population risk	272	33 (10)	31 (10)	-2 (-2 to -1)	<0.001
Two weeks after					
State anxiety (STAI 20-80)[a]					
Increased risk	11	33 (10)	35 (11)	3 (-5 to 10)	0.453
Population risk	175	33 (10)	30 (10)	-3 (-5 to -2)	<0.001
Trait anxiety (STAI 20-80)[a]					
Increased risk	11	35 (11)	35 (12)	0 (-3 to 4)	0.800
Population risk	175	34 (9)	32 (9)	-1 (-2 to -1)	0.002
Depression (HADS 0-22)[b]					

		Increased risk	11	8 (8)	9 (9)	1 (-3 to 6)	0.481
		Population risk	175	7 (5)	7 (6)	-0 (-1 to 0)	0.438

[a] general population mean (SD) 39 (11-13), higher scores refer to more anxiety
[b] clinical significance =>12, higher scores refer to more depression

aOR: adjusted odds ratio, CI: confidence intervals, GP: general practitioner, HADS: hospital anxiety and depression score, OR: odds ratio, RR: relative risk, SD: standard deviation, STAI: state trait anxiety inventory

Supplemental material 4: Summary description of studies excluded for having participants with personal history of cancer

Author, year	Study design	Setting	Personal history of cancer	Participants	Intervention	Comparator	Outcomes
1. Wilson et al. 2005 2. Wilson et al. 2006	Cluster RCT	UK, general practice	Pre-intervention* Breast: 3/185 (2%), Other cancer: 10/185 (5%) Post-intervention* Breast: 6/97 (6%), Other cancer: 4/97 (4%)	Women referred for BC genetic counselling	Intervention package for GP: 1. educational session & materials 2. software (referral guide) 3. email-based link with the cancer genetic clinic	Scottish referral guidelines mailed to all GPs by the Department of Health.	**1. Proportion of GP referral letters categorised as increased risk** **2. Proportion of referred patients confirmed at increased risk by genetic clinic**
MeTree 1. Orlando et al. 2011 2. Orlando et al. 2013 3. Wu et al. 2013 4. Orlando et al. 2014 5. Orlando et al. 2016	Controlled hybrid type two implementation-effectiveness clinical trial (controlled before & after study)	USA, primary care clinics	Colon 3/588 (0.5%), Breast 14/588 (2%), Ovarian 1/588 (0.2%), Hereditary cancer 4/588 (0.7%)	Patients with upcoming well visit	Software to collect personal and family history from patient, stratify risk, generate decision support reports for patient and provider.	Same patients had medical records reviewed at 12 months.	**Agreement between risk level and evidence-based risk management (uptake of preventive strategy)**

BC: breast cancer, GP: general practitioner, RCT: randomised controlled trial * Correspondence with study author