National Institute for Health and Care Excellence

Draft for consultation

Ovarian cancer: identifying and managing familial and genetic risk

[H] Populations with high prevalence

NICE guideline number tbc

Evidence reviews underpinning recommendation 1.4.4 and bullet point 2 in Table 1 in the NICE guideline

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Draft for consultation

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Populations with high prevalence

Review question

Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Introduction

The number of people who have a pathogenic variant that puts them at an increased risk of familial ovarian cancer is not the same across populations. For example, Ashkenazim have a higher incidence of pathogenic variants in *BRCA1* and *BRCA2* genes. As we discover more pathogenic variants that are associated with ovarian cancer, we may also identify new populations in which these variants are common. If the pathogenic variant is common enough within a population, those within the population may be at sufficient risk to be offered genetic testing.

The review investigates which populations are associated with pathogenic variants. Furthermore, the review describes the level of risk seen within these populations and investigates if that risk meets the threshold for genetic testing.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	All people, but subgrouped according to self-reported ancestry. Population groups with high prevalence of pathogenic variants for familial ovarian cancer are of particular interest
Test	Germline pathogenic variant analysis
Comparator	Not applicable
Outcomes	**Critical** Prevalence of pathogenic variants associated with familial ovarian cancer, such as: • *ATM* • *BRCA1* • *BRCA2* • *BRIP1* • *CHEK2* • *PALB2* • *MLH1* • *MSH2* • *MSH6* • *RAD51C* • *RAD51D* • *PMS2* • *DICER1*

- *SMARCA4*

Important

None

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1). Further to these, the committee wanted to see more evidence in other populations such as Polish and Icelandic people which was sparsely available or not available from the included cross-sectional studies, therefore they suggested to include data from case-control studies reporting prevalence of pathogenic variants in relevant populations. Some additional data in the populations of interest was identified and data from the control group (where sample reflected a general population) was reported (matched case-controls were not considered).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Overall 29 studies were included in this review. These are divided into populations with increased risk of high prevalence of pathogenic variants for familial ovarian cancer.

Twenty studies were cross-sectional (Abul-Husn 2019, Anisimenko 2013, Bar-Sade 1997, Bar-Sade 1998, Castillo 2022, Gabai-Kapara 2014, Harboe 2009, Hartge 1999, Kerr 2023, Lieberman 2017, Metcalfe 2020, Pavlovica 2022, Quintana-Murci 2005, Roa 1996, Shiri-Sverdlov 2001, Struewing 1995, Thorlacius 1997, Tiller 2022, Trottier 2016, Zhang 2022), 8 case-control (control arm data used) (Ahearn 2022, Cybulski 2019, Johannesdottir 1996, Lener 2016, Noskowicz 2014, Pelttari 2012, Teodorczyk 2013, Wokolorczyk 2020) and 1 randomized controlled trial (Manchanda 2020). As there was only a sparce or absent evidence on such populations like Polish and Icelandic people from the included cross-sectional studies, data from case-control studies reporting prevalence of pathogenic variants in these populations were included (where sample reflected a general population, matched case-controls were not considered).

The included studies are summarised in Table 2.

The included studies typically reported the prevalence of *BRCA1/2* pathogenic variants, 5 studies reported the prevalence of *CHEK2* (Cybulski 2019, Lener 2016, Pavlovica 2022, Teodorczyk 2013, Wokolorczyk 2020), 3 studies reported the prevalence of *PALB2* (Cybulski 2019, Lener 2016, Noskowicz 2014), 2 studies reported the prevalence of *MSH2/6* (Wokolorczyk 2020, Zhang 2022), 1 study reported the prevalence of *RAD51D* (Pelttari 2012), one study reported the prevalence of *ATM* (Wokolorczyk 2020) and 1 study reported the prevalence of *MLH1 and PMS2* (Zhang 2022) pathogenic variants.

Most studies were conducted in Israel, the USA and Poland, and most included various Jewish populations: Ashkenazi Jews (Abul-Husn 2019, Castillo 2022, Gabai-Kapara 2014, Hartge 1999, Lieberman 2017, Manchanda 2020, Metcalfe 2020, Roa 1996, Struewing 1995, Tiller 2022), Iraqi Jews (Bar-Sade 1997, Shiri-Sverdlov 2001) and non-Ashkenazi Israeli Jews (Bar-Sade 1998). Other studies reported the prevalence of *BRCA1/2* pathogenic variants in African Americans (Abul-Husn 2019), Polish people (Cybulski 2019, Lener 2016, Wokolorczyk 2020), Russians (Anisimenko 2013), Greenlanders (Harboe 2009), Icelanders

(Johannesdottir 1996, Thorlacius 1007), Orcadians (Kerr 2023), Ghanaians (Ahearn 2022) and Bahamians (Trottier 2016).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Outcomes
Abul-Husn 2019 Cross-sectional USA	N=6874 African American N=3889 Ashkenazi Jews Age (median (range), years): 59 (45-70) Gender: women 59.3%	• Prevalence of *BRCA1/2* pathogenic variants
Ahearn 2022 Case-control Ghana	N=1563 Ghanaians in Ghana Age (mean (SD), years): 45.8 (12.7) Gender: women	• Prevalence of: ○ *ATM* ○ *BRCA1/2* ○ *BRIP1* ○ *CHEK2* ○ *PALB2* ○ *MLH1* ○ *MLH2* ○ *MSH2* ○ *MSH6* ○ *RAD51C* ○ *RAD51D* ○ *PMS2* pathogenic variants
Anisimenko 2013 Cross-sectional Russia	N=7920 Russians in Russia Age (mean (SD), years): 53.8 (7), range 46-69 Gender: NR	• Prevalence of *BRCA1* pathogenic variant
Bar-Sade 1997 Cross-sectional Israel	N=639 Iraqi-Jewish population (Iraqi-born) in Israel Age (years, range): 32-93 Gender: women 51.5%	• Prevalence of *BRCA1* pathogenic variant
Bar-Sade 1998 Cross-sectional Israel	N=704 non-Ashkenazi Israeli Jews of: n=354 Moroccan origin n=200 Yemenite origin n=150 Iranian origin Age and gender: NR	• Prevalence of *BRCA1* pathogenic variant
Castillo 2022	N=327 Ashkenazi Jews in Uruguay	• Prevalence of *BRCA1*

Study	Population	Outcomes
Cross-sectional Uruguay	Age categories (years, n): <40=86 (26.3%), >=40 to <60=174 (53.2%), >=60=67 (20.5%) Gender: women 95.4%	pathogenic variant
Cybulski 2019 Case-control Poland	N=2036 Polish people in Poland Age and gender: NR	• Prevalence of: ○ *BRCA1* ○ *CHEK2* ○ *PALB2* pathogenic variants
Gabai-Kapara 2014 Cross-sectional Israel	N=8195 Ashkenazi Jews in Israel Age: NR Gender: men 100%	• Prevalence of *BRCA1/2* pathogenic variants
Harboe 2009 Cross-sectional Greenland	N=1071 Greenlandic Inuit origin population in Greenland Age and gender: NR	• Prevalence of *BRCA1* pathogenic variant
Hartge 1999 Cross-sectional USA	N=5318 Ashkenazi Jews in the USA Age categories (in those without cancer, years (n)): 21-39=915, 40-59=2684, >=60=1363 Gender: women 70.4%	• Prevalence of *BRCA1/2* pathogenic variants
Johannesdottir 1996 Case-control Iceland	N=499 Icelanders in Iceland Age and gender: NR	• Prevalence of *BRCA2* pathogenic variants
Kerr 2023 Cross-sectional UK	N=2088 Orcadians in the Northern Isles of Scotland, UK Age and gender: NR	• Prevalence of *BRCA1* pathogenic variant
Lener 2016 Case-control Poland	N=4000 Polish people in Poland Age and gender: NR	• Prevalence of: ○ *BRCA1* ○ *CHEK2* ○ *PALB2* pathogenic variants
Lieberman 2017 Cross-sectional Israel	N=1771 Ashkenazi Jews in Israel Age (mean (SD), years): 52 (13) Gender: women 79%	• Prevalence of *BRCA1/2* pathogenic variants
Manchanda 2020 RCT (data were analysed as observational and not as randomised data)	N=1034 Ashkenazi Jews in the UK Age (mean (SD), years): family history group n=54.3 (14.31), population screening group n=54.3 (14.99)	• Prevalence of *BRCA1/2* pathogenic variants

Study	Population	Outcomes
UK	Gender: women 66.8%	
Metcalfe 2020 Cross-sectional Canada	N=2080 Ashkenazi/Sephardic Jews in Canada Age (mean (range), years): 49.3 (24-79) Gender: women 100%	• Prevalence of *BRCA1/2* pathogenic variants
Noskowicz 2014 Case-control Byelorussia, Germany and Russia	N=1242 Byelorussians in Byelorussia N=989 Germans in Germany N=596 Russians in Russia Age and gender: NR	• Prevalence of *PALB2* pathogenic variant
Pavlovica 2022 Cross-sectional Estonia	N=4776 Estonians in Estonia Age (mean, years): 49.3 (24-79) Gender: women 47%	• Prevalence of *CHEK2* pathogenic variant
Pelttari 2012 Case-control Finland	N=2102 Finns in Finland Age and gender: NR	• Prevalence of *RAD51D* pathogenic variant
Quintana-Murci 2005 Cross-sectional Israel	N=442 Iranian non-Jews in Israel Age: NR Gender: men 100%	• Prevalence of *BRCA1* pathogenic variant
Roa 1996 Cross-sectional Israel, USA	N=between 398 and 403 Ashkenazi Jews in Israel N=between 2687 and 2717 Ashkenazi Jews in the US* *sample size differs for different *BRCA1* mutations tested Age and gender: NR	• Prevalence of *BRCA1* pathogenic variant
Shiri-Sverdlov 2001 Cross-sectional Israel	N=289 Iraqi Jews in Israel Age: NR Gender: women 66.8%	• Prevalence of *BRCA1* pathogenic variant
Struewing 1995 Cross-sectional Israel, USA	N=858 Ashkenazi Jews in Israel and the US Age and gender: NR	• Prevalence of *BRCA1* pathogenic variant
Teodorczyk 2013 Case-control	N=8302 Polish people in Poland Age (mean (SD), years): men 61.2 (23-90), women 52.2 (19-91)	• Prevalence of *CHEK2* pathogenic variant

Study	Population	Outcomes
Poland	Gender: 52%	
Thorlacius 1997 Cross-sectional Iceland	N=520 Icelanders in Iceland Age and gender: NR	• Prevalence of *BRCA2* pathogenic variant
Tiller 2022 Cross-sectional Australia	N=2167 (tested, overall N=2274) Jews in Australia of which 94.5% Ashkenazi, 7.8% Sephardic Age (mean (SD), years): 48 (14) Gender: women 25.3%	• Prevalence of *BRCA1/2* pathogenic variants
Trottier 2016 Cross-sectional Bahamas	N=1089 Bahamians in Bahamas Age: NR Gender: women 100%	• Prevalence of *BRCA1/2* pathogenic variants
Wokolorczyk 2020 Case-control Poland	N=308 Polish people in Poland Age (mean (range), years): women: 56.9 (40-84); men: 62.1 (45-89) Gender: women 52%	• Prevalence of: ○ *ATM* ○ *BRCA1/2* ○ *CHEK2* ○ *MSH2* ○ *MSH6* pathogenic variants
Zhang 2022 Cross-sectional China, Macau, Singapore	N=18844 Ethnic Chinese population of which 61.8% mainland Chinese, 23.6% Macau Chinese, 14.6% Singapore Chinese Age and gender: NR	• Prevalence of: ○ *MLH1* ○ *MSH2/6* ○ *PMS2* pathogenic variants

NR: not reported; SD: standard deviation

See the full evidence tables in appendix D and forest plots in Appendix E.

Summary of the evidence

Prevalence of *ATM* pathogenic variants

Polish population

There was moderate quality evidence that the *ATM* prevalence in Polish people in Poland was 0% (0% to 1.30%).

Ghanaian population

There was high quality evidence that the *ATM* prevalence in Ghanaians from Ghana was 0.32% (0.14% to 0.75%).

Prevalence *of BRAC1* pathogenic variants

Ashkenazi Jewish population

Most of the evidence was in Ashkenazi Jewish people. There was moderate quality evidence that the overall *BRCA1* prevalence in Ashkenazi Jewish people was 1.15% (0.93% to 1.40%).

Ashkenazi/Sephardic Jewish population

There was high quality evidence that the *BRCA1* prevalence in Ashkenazi/Sephardic Jewish people in Canada was 0.48% (0.23% to 0.88%).

Ghanaian population

There was high quality evidence that the *BRCA1* prevalence in Ghanaians from Ghana was 0.19% (0.04% to 0.56%).

Greenlandic women and Greenlandic people of Inuit family background

There was moderate quality evidence that the *BRCA1* prevalence in pregnant women in Greenland was 1.61% (1.08% to 2.31%) and people from Greenland of Inuit family background was 9.71% (8.00% to 11.64%).

Iranian non-Jewish population

There was moderate quality evidence that the *BRCA1* prevalence in Iranian non-Jewish people in Israel was 0% (0% to 0.83%).

Iraqi Jewish population

There was moderate quality evidence that the *BRCA1* prevalence in Iraqi Jewish people in Israel was 0.70% (0.31% to 1.54%).

Non-Ashkenazi Jewish population

There was very low to low quality evidence that the *BRCA1* prevalence in non-Ashkenazi Jewish people of Iranian origin in Israel was 0% (0% to 2.43%), Moroccan origin was 1.13% (0.31% to 2.87%) and Yemenite origin was 0% (0% to 1.83%).

Orcadians

There was high quality evidence that the *BRCA1* prevalence in Orcadians from the Northern Isles of Scotland was 0.96% (0.59% to 1.48%).

Polish population

There was moderate quality evidence that the overall *BRCA1* prevalence in Polish people in Poland was 0.45% (0.33% to 0.62%).

Russian population

There was moderate quality evidence that the *BRCA1* prevalence in Russians in Russia was 0.30% (0.19% to 0.45%).

Prevalence *of BRAC2* pathogenic variants

Ashkenazi Jewish population

There was low quality evidence that the overall *BRCA2* prevalence in Ashkenazi Jewish people in Israel and the USA was 1.42% (0.49% to 4.07%).

Ashkenazi/Sephardic Jewish population

There was high quality evidence that the *BRCA2* prevalence in Ashkenazi/Sephardic Jewish people in Canada was 0.58% (0.30% to 1.01%).

Ghana population

There was moderate quality evidence that the *BRCA2* prevalence in Ghanaians from Ghana was 0.51% (0.22% to 1.01%).

Icelandic population

There was moderate quality evidence that the overall *BRCA2* prevalence in Icelanders in Iceland was 0.50% (0.05% to 4.67%).

Polish population

There was moderate quality evidence that the *BRCA2* prevalence in Polish people in Poland was 0% (0% to 1.19%).

Prevalence *of BRAC1/2* pathogenic variants

African American or African population

There was high quality evidence that the *BRCA1/2* prevalence in African Americans or Africans in the USA was 0.45% (0.31% to 0.64%).

Ashkenazi Jewish population

There was high quality evidence that the overall *BRCA1/2* prevalence in Ashkenazi Jewish people in Israel, the UK and the USA was 2.19% (1.99% to 2.40%).

Ashkenazi/Sephardic Jewish population

There was high quality evidence that the *BRCA1/2* prevalence in Ashkenazi/Sephardic Jewish people in Canada and Australia was 1.18% (0.90% to 1.56%).

Bahamian population

There was high quality evidence that the *BRCA1/2* prevalence in Bahamians in the Bahamas was 0.09% (0% to 0.51%).

Prevalence of *BRIP1* pathogenic variants

Ghanaian population

There was high quality evidence that the *BRIP1* prevalence in Ghanaians from Ghana was 0.13% (0.14% to 0.47%).

Prevalence of *CHEK2* pathogenic variants

Estonian population

There was moderate quality evidence that the *CHEK2* prevalence in Estonians in Estonia was 9.32% (8.51% to 10.18%).

Ghanaian population

There was high quality evidence that the *CHEK2* prevalence in Ghanaians from Ghana was 0.06% (0% to 0.36%).

Polish population

There was very low quality evidence that the overall *CHEK2* prevalence in Polish people in Poland was 3.37% (0.77% to 13.63%).

Prevalence of *PALB2* pathogenic variants

Polish population

There was moderate quality evidence that the overall *PALB2* prevalence in Polish people in Poland was 0.21% (0.13% to 0.33%).

Byelorussian population

There was moderate quality evidence that the *PALB2* prevalence in Byelorussians in Byelorussia was 0% (0% to 0.30%).

German population

There was moderate quality evidence that the *PALB2* prevalence in Germans in Germany was 0% (0% to 0.40%).

Russian population

There was moderate quality evidence that the *PALB2* prevalence in Russians in Russia was 0% (0% to 0.70%).

Ghanaian population

There was high quality evidence that the *PALB2* prevalence in Ghanaians from Ghana was 0.06% (0.01% to 0.35%).

Prevalence of *MLH1, MSH2/6, PMS2* pathogenic variants

Chinese population

There was moderate quality evidence that the *MLH1, MSH2/6, PMS2* prevalence in ethnic Chinese in mainland China, Macau and Singapore was 0.20% (0.19% to 0.20%).

Polish population

There was moderate quality evidence that the *MSH2* and *MSH6* prevalence in Polish people in Poland was 0% (0% to 1.30%).

Ghanaian population

There was high quality evidence that the *MLH1* prevalence in Ghanaians in Ghana was 0% (0% to 0.30%), *MSH2* prevalence was 0.06% (0.01% to 0.35%), *MSH6* prevalence was 0.19% (0.06% to 0.56%) and *PMS2* prevalence was 0% (0% to 0.002%).

Prevalence of *RAD51C* pathogenic variants

Ghanaian population

There was high quality evidence that the *RAD51C* prevalence in Ghanaians from Ghana was 0.06% (0.01% to 0.35%).

Prevalence of *RAD51D* pathogenic variants

Finish population

There was moderate quality evidence that the *RAD51D* prevalence in Finns in Finland was 0.05% (0% to 0.30%).

Ghanaian population

There was high quality evidence that the *RAD51D* prevalence in Ghanaians from Ghana was 0% (0% to 0.30%).

See appendix F for full GRADE tables.

Economic evidence

Included studies

Four economic studies were identified which were relevant to this review (Manchanda 2015, Manchanda 2017, Michaelson-Cohen 2022, Patel 2018).

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

The systematic search of the economic literature undertaken for the guideline identified the following studies:

- One UK cost-utility analysis on population *BRCA1/BRAC2* testing in Sephardi Jewish women (Patel 2018);
- One UK cost-utility analysis on *BRCA1/BRCA2* testing in Ashkenazi Jewish women with one to four Ashkenazi Jewish grandparents (Manchanda 2017);
- One UK cost-utility analysis on population *BRCA1/BRCA2* testing in Ashkenazi Jewish women (Manchanda 2015);
- One Israeli cost-utility analysis on population *BRCA1/BRAC2* testing in Ashkenazi Jewish women (Michaelson-Cohen 2022).

See the economic evidence tables in appendix H. See Table 3 for the economic evidence profiles of the included studies.

Table 3: Economic evidence profiles for *BRCA1/BRAC2* genetic testing (versus clinical or family history-based genetic testing) for Jewish women unaffected by cancer:

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
Patel 2018 UK Cost-utility analysis	Minor [2]	Directly [3]	Modelling study (Markov) Population: Sephardi Jewish women aged ≥30 years Time horizon: Lifetime (extending to 83 years) Outcome: QALYs	£67.04	1.0006	£67.04	- Probability of being cost-effective: 100% at the £20k/QALY gained. - The model was most sensitive to *BRCA1* mutation prevalence estimates in the Sephardi population and family history positive individuals. However, the conclusions were unchanged and the ICER of genetic testing remained below £20k/QALY gained. - The conclusions were unchanged in scenario analyses where no benefit in breast cancer risk reduction from undergoing a risk-reducing oophorectomy (RRSO) was modelled, no HRT was offered or a lower risk-reducing mastectomy (RRM) rate of 13% (base case: 0.60) and RRSO rate of 49% (base-case: 0.66) was modelled.
Manchanda 2017 UK	Minor [4]	Directly [5]	Modelling study (Markov) Population: Ashkenazi Jewish	Grandparents: Four -£94	Grandparents: Four 0.032	Dominant in women with four to two AJ grandparents	- For populations with four, three, two or one AJ grandparent(s) the probability of genetic testing being cost-

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
Cost-utility analysis			(AJ) women ≥30 years with four to one AJ grandparents. Time horizon: Lifetime (extending till the age of 83 years) Outcome: QALYs	Three -£62 Two -£26 One £13	Three 0.027 Two 0.021 One 0.015	£863/QALY in women with one AJ grandparent	effective was ≥95% at the £20k/QALY gained threshold. - The conclusions remained unchanged in scenario analyses where no benefit with premenopausal RRSO on reduction in breast cancer risk (base case: 0.49) was modelled, a lower RRM rate of 13% (base case: 0.52) as reported in Israeli women was used or assuming 20% risk-reducing surgery uptake (base case: RRSO=0.55, RRM=0.52).
Manchanda 2015 UK Cost-utility analysis	Minor [6]	Directly [7]	Modelling study (Markov) Population: AJ women aged ≥30 years Time horizon: Lifetime Outcome: QALYs	-£64	0.031	Dominant	-Probability of being cost-effective was 94% at £20k/QALY gained threshold. - The conclusions were robust to changes in utility values, costs, penetrance estimates and rate of uptake of preventive/risk-reducing surgery. - The model was highly sensitive to the overall *BRCA* prevalence and *BRCA* prevalence in family history negative women. However, the conclusions remained unchanged and the genetic testing remained either dominant or resulted in an

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	QALYs	Cost effectiveness (Cost/QALY)	
							ICER < £20k/QALY gained. - The genetic testing remained dominant when modelling breast cancer prophylaxis with SERMs (tamoxifen/raloxifene) in *BRCA* carriers. - Conclusions were unchanged in a scenario where women opt for genetic testing at age 50 (average age of menopause) with a median age for RRSO and RRM at 54 years (just below the weighted average age of ovarian cancer onset in *BRCA1/BRCA2* carriers).
Michaelson-Cohen 2022 Israel Cost-utility analysis	Potentially serious [8]	Partially [9]	Modelling study (Decision tree) Population: AJ women aged 30 years Time horizon: Lifetime Outcome: QALYs	£187	0.006	£31,167	-Probability of genetic testing being cost-effective was 0.50 at WTP of £30,963/QALY. - The ICER of genetic testing was sensitive to the carrier prevalence in AJ population and testing rates (resulted in ICERs > £137,612/QALY). Also sensitive to BC reduction post RRSO, OC risk in carriers and OC risk reduction post RRSO with ICERs approaching £68,806/QALY.

Abbreviations: AJ: Ashkenazi Jewish; HRT: Hormone replacement therapy; ICER: Incremental cost-effectiveness ratio; k: Thousand; QALY: Quality-adjusted life-years; RRM: Risk reducing mastectomy; RRSO: Risk reducing salpingo-oophorectomy; SERM: Selective Estrogen Receptor Modulators; UK: United Kingdom

[1] Costs were converted to UK pounds using OECD purchasing power parities (PPPs)
[2] Well conducted study and no notable limitations
[3] UK study, QALYs
[4] Overall well conducted study, limited deterministic sensitivity analyses
[5] UK study, QALYs
[6] Well conducted study and no notable limitations
[7] UK study, QALYs
[8] Unclear reporting, for example, presentation of incremental analysis was unclear making the interpretation of sensitivity analyses difficult; included uptake rates in an index population; unclear time horizon of the analysis
[9] Israeli study

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Economic

- Evidence from a cost-utility analysis based on modelling (Patel 2018) suggests that *BRCA* genetic testing is likely to be cost effective compared with clinical criteria/family history-based *BRCA* genetic testing in adult Sephardi Jewish women in the UK. The study is directly applicable to NICE's decision making context and has minor limitations.
- Evidence from a cost-utility analysis based on modelling (Manchanda 2017) suggests that *BRCA* genetic testing is likely to be cost effective compared with clinical criteria/family history-based *BRCA* genetic testing in adult Ashkenazi Jewish women with varying degrees of Ashkenazi Jewish ancestry (ranging from four to one Ashkenazi Jewish grandparents) in the UK. The study is directly applicable to NICE's decision making context and has minor limitations.
- Evidence from a cost-utility analysis based on modelling (Manchanda 2015) suggests that *BRCA* genetic testing is likely to be cost effective compared with clinical criteria/family history-based *BRCA* genetic testing in adult Ashkenazi Jewish women in the UK. The study is directly applicable to NICE's decision making context and has minor limitations.
- Evidence from a cost-utility analysis based on modelling (Michaelson-Cohen 2022) suggests that *BRCA* genetic testing is unlikely to be cost effective compared with clinical criteria/family history-based *BRCA* genetic testing and cascade testing in adult Ashkenazi Jewish women in Israel. The study is partially applicable to NICE's decision making context and has potentially serious limitations.

The committee's discussion of the evidence

The outcomes that matter most

The committee were interested in the prevalence of various pathogenic variants associated with familial ovarian cancer and choose them as critical outcomes.

The quality of the evidence

The quality of the evidence from the included studies was assessed with GRADE and ranged from very low to high, with most of the evidence being of a moderate quality. This was predominately due to serious overall risk of bias in some outcomes; imprecision around the effect estimate in a few outcomes and the presence of serious or very serious heterogeneity in a few outcomes, which was unresolved by subgroup analysis.

There was no evidence identified for the prevalence of pathogenic variants in *DICER1* and *SMARCA4* in specific populations.

Benefits and harms

At-risk populations

Based on the evidence, the committee decided to recommend genetic counselling and genetic testing for people from Ashkenazi Jewish and Greenlandic populations because these populations had the highest prevalence rates for *BRCA1* and *BRCA2* pathogenic variants. Of all the pathogenic variants in the protocol *BRCA1* and *BRCA2* also carry the

highest risk associated with ovarian cancer. Greenlanders, even though a very small minority in the UK, have a high prevalence rate as well and the committee agreed to include them in the recommendation to make healthcare professionals aware of their increased risk. The clinical evidence was less clear about people with a Jewish Sephardi family background. The evidence usually combined them with the Ashkenazi group which makes it somewhat unclear which prevalence applied to them as an individual group, but the rates were generally lower. Even though prevalence seemed to have been lower than in Ashkenazi or Greenlandic populations, the committee referred to economic studies (see below) which showed genetic counselling and genetic testing of Ashkenazi and Sephardi Jewish populations to be cost effective. They decided based on this to extend the offer of genetic counselling and genetic testing to the Jewish Sephardi population.

The committee discussed that studies reporting the prevalence of pathogenic variants in Jewish populations usually do not undertake the whole genome sequencing as they target specific founder variants. A founder genetic variant is an alteration observed with high frequency in a group that is or was geographically or culturally isolated, in which 1 or more of the ancestors was a carrier of the altered gene. Testing for only the founder variant is more efficient and less costly than testing the whole genome.

In the protocol for this evidence review the committee intentionally kept the list of pathogenic variants broad. They therefore agreed that this needs to be considered in line with which pathogenic variant should be captured on a genetic test panel (evidence review J). In relation to other genes and other population, based on evidence review J they noted that ATM and CHEK2 did not appear to be closely associated with ovarian cancer and they are currently also not listed in the UK national genomic test directory in relation to ovarian cancer. They therefore did not recommend testing of the populations that were listed for these two variants. Whilst there were other populations with *BRCA1* or *BRCA2* pathogenic variants the committee discussed that for many of them the point estimate of the prevalence was quite low even if there was some overlap in confidence intervals (suggesting that potentially the number of cases within the sample was low leading to wide confidence intervals). This combined with the fact that there was no economic evidence supporting testing of these entire populations meant that the committee was not confident enough to comment on these given also that it would mean a big initial resource impact to implement this on limited information. Whilst other reported genes are associated with ovarian cancer in line with evidence report J (*BRIP1, PALB2, RAD51C, RAD51D MLH1, MSH2 and MSH6*) *PMS2* is associated with endometrial cancer alone therefore not relevant in the context of ovarian cancer. The committee discussed that evidence needs to be considered in relation to lifetime risk associated with a particular pathogenic variant. The committee noted that the lifetime risk associated with *BRIP1, PALB2, RAD51C, RAD51D MLH1, MSH2* and *MSH6* pathogenic variants is lower than for *BRCA1* and *BRCA2.* They noted that this information was available from the UK cancer genetics group. Having a lower lifetime risk would mean that a considerable larger prevalence would be needed to make this an effective or cost effective strategy at a population level. Without such data the committee did not feel confident to suggest thresholds for population testing related to these pathogenic variants.

Information provision

The committee noted that people from these populations may not be aware that they may have an increased risk of having a pathogenic variant when they visit healthcare professionals. They emphasised that information needs to be given to them so that they know why there is this risk and what the next steps may be so that they can make an informed decision about genetic counselling and genetic testing.

Cost effectiveness and resource use

The committee explained that the ovarian cancer risk associated with a pathogenic variant would be similar in, for example, Jewish and non-Jewish carriers. That is, any excess risk of

ovarian cancer in Jewish women with a family history of ovarian cancer would be largely attributable to mutations in *BRCA*.

The committee explained that the prevalence of pathogenic variants in Ashkenazi/Sephardi Jewish and Greenlandic populations aligned with the carrier probability identified by de-novo modelling undertaken for this guideline, at which offering genetic testing to people with a family history of cancer suggestive of pathogenic variants in ovarian cancer predisposition genes was found to be cost-effective (for methods and results, please see evidence review F on carrier probability for genetic testing in unaffected individuals).

For example, the de-novo modelling found that in females aged 30-49, offering genetic counselling and testing was found to be cost-effective if the probability of having a pathogenic variant was 2% or higher. In those aged 50-59, the threshold was 3% or higher, in those aged 60-69, it was 6% or higher, and in those aged 70 or over it was 10% or higher.

The committee explained that the majority of eligible people for population testing would be aged under 60 and that the cost-effective carrier probabilities in these age groups align with the prevalence of ovarian cancer in, for example, Ashkenazi Jewish population, where the prevalence is approximately 3%.

There was also existing economic evidence from three studies conducted in the UK. The committee noted that all studies found *BRCA* genetic testing of all Sephardi or Ashkenazi Jewish women was cost-effective, compared to clinical or family history-based criteria. The committee discussed some of the limitations associated with the existing economic evidence. For example, genetic counselling in one of the studies was done using the DVD format followed by shorter face-to-face counselling. This may not represent current practice for all services. It was also noted that some of the model inputs may be outdated due to the studies being a few years old and none of the modelling studies considered treatment with PARP inhibitors.

Also, the committee highlighted that all UK studies were conducted by the same academic group and used similar assumptions. They expressed concerns about the generalisability of these findings. Despite the above limitations associated with the existing economic evidence the incremental cost-effectiveness ratios in all included UK economic studies were substantially below the lower NICE cost-effectiveness threshold of £20,000 per quality-adjusted life year (QALY) gained. Large changes in costs would be required to reverse the conclusions from these studies.

An additional Israeli study on genetic testing for all Ashkenazi Jewish women exceeded NICE's upper cost-effectiveness threshold of £30,000 per QALY gained. However, the committee noted that this study was only partially applicable to NICE's decision-making context and that it had potentially serious limitations, such as an unclear time horizon and the fact that the study included genetic testing uptake in the index population, which is not relevant to the decision problem.

The committee also noted that the existing economic evidence relates primarily to *BRCA* genetic testing. However, the recommendation in this area will mean testing for other genes included in the panel as well. The committee explained that the *BRCA* genes, due to their high prevalence, are driving the cost-effectiveness of genetic testing.

The committee acknowledged that implementing population testing in high-risk populations, which is not current practice, will have a resource impact. Initially, this might be challenging due to the need to invite the entire population for testing but after the first wave, numbers would decrease, easing the pressure on services. This will also increase demand on existing services, such as psychological and menopause support.

The committee noted that despite these challenges, population testing would identify more individuals for risk management which is a cost-effective strategy. The committee noted that there are currently some pilot projects in the NHS (for example, the NHS Jewish BRCA

testing programme as well as a published programme model: A collaborative genetic carrier screening model for the British Ashkenazi Jewish community), and linking up with these projects could facilitate implementation, making the process easier, because some of the pathways into the services would already be established.

The committee concluded that the combined evidence from the existing UK economic studies, de-novo modelling undertaken for this guideline regarding threshold carrier probabilities for genetic testing and the pilot NHS programme for the Jewish community provided sufficient support for genetic testing in Ashkenazi/Sephardi Jewish and Greenlandic populations.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.4 and bullet point 2 in Table 1 in the NICE guideline.

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Effectiveness

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Appendices

Appendix A Review protocol

Review protocol for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022351098
1.	Review title	Populations with a high prevalence of pathogenic variants for familial ovarian cancer
2.	Review question	Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?
3.	Objective	To determine whether there are populations with a high enough prevalence of pathogenic variants for familial ovarian cancer that they could be routinely offered genetic testing, instead of first assessing their carrier probability
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • International Health Technology Assessment (INAHTA) database Searches will be restricted by: • English language studies • Human studies The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for

		inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	**Inclusion**: All people, but subgrouped according to self-reported ancestry. Population groups with high prevalence of pathogenic variants for familial ovarian cancer are of particular interest.
7.	Test	Germline pathogenic variant analysis
8.	Comparator	Not applicable
9.	Types of study to be included	• Cross sectional studies
10.	Other exclusion criteria	**Inclusion**: • Full text papers **Exclusion**: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/ study quality • Non-English language articles
11.	Context	Not applicable – no changes to scope question or existing guidance to be updated
12.	Primary outcomes (critical outcomes)	Prevalence of pathogenic variants associated with familial ovarian cancer, such as: • *ATM* • *BRCA1* • *BRCA2* • *BRIP1*

		• *CHEK2* • *PALB2* • *MLH1* • *MSH2* • *MSH6* • *RAD51C* • *RAD51D* • *PMS2* • *DICER1* • *SMARCA4*
13.	Secondary outcomes (important outcomes)	
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records (or 300 records whichever is smaller); 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. The full set of records will not be dual screened because the population, interventions and relevant study designs are relatively clear and should be readily identified from titles and abstracts. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality

		assessed by a senior reviewer
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists: o JBI Checklist for prevalence studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses or prevalence data will be done with a random effects model. Prevalence rates with 95% CIs will be used as the outcome. Validity The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/
17.	Analysis of sub-groups	Evidence will be stratified by: Self-reported ancestry, for example: o Ashkenazi Jewish o Polish o Icelandic o Afrikaner o Sephardi Jewish Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:

		Groups identified in the equality considerations section of the scope • socioeconomic and geographical factors • age • ethnicity • disabilities • people for whom English is not their first language or who have other communication needs • trans people (particularly trans men) • non-binary people Where evidence is stratified or subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery

		☒ Other (prevalence)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	November 2022		
22.	Anticipated completion date	13 March 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** National Institute for Health and Care Excellence (NICE) **5b Named contact e-mail** focl@nice.org.uk **5e Organisational affiliation of the review** NICE		

25.	Review team members	Senior Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)
26.	Funding sources/sponsor	This systematic review is being completed by NICE
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022351098
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Genetic testing, familiar ovarian cancer

33.	Details of existing review of same topic by same authors		
34.	Current review status	☒ ☐ ☐ ☐ ☐	Ongoing Completed but not published Completed and published Completed, published and being updated Discontinued
35.	Additional information		
36.	Details of final publication	https://www.nice.org.uk	

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Appendix B Literature search strategies

Literature search strategies for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Database: Ovid MEDLINE ALL

Date of last search: 25/01/2023

#	Searches
1	exp Ovarian Neoplasms/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).ti,ab,kf.
3	or/1-2
4	exp Breast Neoplasms/
5	exp "Neoplasms, Ductal, Lobular, and Medullary"/
6	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).ti,ab,kf.
7	or/4-6
8	3 or 7
9	exp Genetic Predisposition to Disease/
10	Pedigree/
11	exp Neoplastic Syndromes, Hereditary/
12	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).ti,ab,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).ti,ab,kf.
14	HNPCC.ti,ab,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).ti,ab,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).ti,ab,kf.
17	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).ti,ab,kf.
18	gardner* syndrome*.ti,ab,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).ti,ab,kf.
20	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).ti,ab,kf.
21	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).ti,ab,kf.
22	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).ti,ab,kf.
23	risk factors/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).ti,ab,kf.
25	((carrier* or gene*) adj3 mutat*).ti,ab,kf.
26	exp Genes, Tumor Suppressor/
27	exp Tumor Suppressor Proteins/
28	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).ti,ab,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).ti,ab,kf.
30	or/9-29
31	8 and 30
32	exp Fanconi Anemia Complementation Group Proteins/
33	(Fanconi An?emia adj3 protein*).ti,ab,kf.
34	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).ti,ab,kf.
35	("breast cancer gene 1" or "breast cancer gene 2").ti,ab.
36	Rad51 Recombinase/

#	Searches
37	Ataxia Telangiectasia Mutated Proteins/
38	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).ti,ab,kf.
39	Checkpoint Kinase 2/
40	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).ti,ab,kf.
41	Carcinoma, Small Cell/ge [Genetics]
42	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
43	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
44	exp Sertoli-Leydig Cell Tumor/
45	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
46	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
47	Epithelial Cell Adhesion Molecule/
48	Epithelial cell adhesion molecule*.tw,kf.
49	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
50	or/32-49
51	31 or 50
52	Genetics, Population/ or founder effect/ or Cultural Characteristics/
53	exp Population Groups/ge [Genetics]
54	((population or founder or cultur*) adj2 (dynamic* or genetic* or effect* or group* or character* or general)).ti,ab,kf.
55	Jews/
56	(ethnic* or ancestr* or religio* or jew or jews or jewish or ashkenazi* or sephardi* or sefardi* or polish or poles or poland or afrikaner* or icelandic* or iceland).ti,ab,kf.
57	or/52-56
58	Mass Screening/ or "Early Detection of Cancer"/
59	((population* or mass or cancer*) adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or diagnos* or identif* or predict* or frequenc*)).ti,ab,kf.
60	Germ-Line Mutation/
61	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*) adj3 (test* or analys?s or assess* or evaluat*)).ti,ab,kf.
62	exp Genetic Testing/
63	(genetic adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)).ti,ab,kf.
64	exp Sequence Analysis/
65	((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) adj2 (sequenc* or technique* or technolog* or method* or applicat*)).ti,ab,kf.
66	((sanger or dna) adj2 (sequenc* or method* or technique* or technolog* or applicat*)).ti,ab,kf.
67	chain termination method*.ti,ab,kf.
68	((multi* adj3 probe amplification*) or MLPA).ti,ab,kf.
69	(next generation sequenc* or NGS).ti,ab,kf.
70	exp risk assessment/ or risk factors/
71	((risk* or probabil*) adj3 (high* or increas* or factor* or rais* or low* or reduc* or assess* or predict* or analys?s)).ti,ab,kf.
72	or/58-71
73	57 and 72
74	51 and 73
75	letter/
76	editorial/
77	news/
78	exp historical article/
79	Anecdotes as Topic/
80	comment/
81	case reports/
82	(letter or comment*).ti.

#	Searches
83	or/75-82
84	randomized controlled trial/ or random*.ti,ab.
85	83 not 84
86	animals/ not humans/
87	exp Animals, Laboratory/
88	exp Animal Experimentation/
89	exp Models, Animal/
90	exp Rodentia/
91	(rat or rats or mouse or mice or rodent*).ti.
92	or/85-91
93	74 not 92
94	limit 93 to English language
95	Meta-Analysis/
96	Meta-Analysis as Topic/
97	(meta analy* or metanaly* or metaanaly*).ti,ab.
98	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
99	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
100	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
101	(search* adj4 literature).ab.
102	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
103	cochrane.jw.
104	or/95-103
105	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt.
106	drug therapy.fs.
107	(groups or placebo or randomi#ed or randomly or trial).ab.
108	Clinical Trials as Topic/
109	trial.ti.
110	or/105-109
111	Observational Studies as Topic/
112	Observational Study/
113	Epidemiologic Studies/
114	exp Case-Control Studies/
115	exp Cohort Studies/
116	Cross-Sectional Studies/
117	Controlled Before-After Studies/
118	Historically Controlled Study/
119	Interrupted Time Series Analysis/
120	Comparative Study.pt.
121	case control$.tw.
122	case series.tw.
123	(cohort adj (study or studies)).tw.
124	cohort analy$.tw.
125	(follow up adj (study or studies)).tw.
126	(observational adj (study or studies)).tw.
127	longitudinal.tw.
128	prospective.tw.
129	retrospective.tw.
130	cross sectional.tw.
131	or/111-130
132	94 and (104 or 110 or 131)

1 Database: Ovid Embase

2 Date of last search: 25/01/2023

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp breast tumor/
5	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
6	or/4-5
7	3 or 6
8	exp genetic predisposition/
9	pedigree/
10	exp hereditary tumor syndrome/
11	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
12	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
13	HNPCC.tw,kf.
14	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
15	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
16	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
17	gardner* syndrome*.tw,kf.
18	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
19	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
20	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
21	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
22	risk factor/
23	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
24	((carrier* or gene*) adj3 mutat*).tw,kf.
25	tumor suppressor gene/
26	exp tumor suppressor protein/
27	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
28	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
29	or/8-28
30	7 and 29
31	Fanconi anemia protein/
32	(Fanconi An?emia adj3 protein*).tw,kf.
33	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
34	("breast cancer gene 1" or "breast cancer gene 2").tw.
35	Rad51 protein/
36	ATM protein/
37	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
38	checkpoint kinase 2/
39	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
40	small cell carcinoma/
41	genetics/

#	Searches
42	40 and 41
43	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
44	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
45	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
46	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
47	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
48	epithelial cell adhesion molecule/
49	Epithelial cell adhesion molecule*.tw,kf.
50	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
51	or/31-39,42-50
52	30 or 51
53	*population genetics/ or *founder effect/ or *cultural factor/
54	exp *population group/
55	*genetics/
56	54 and 55
57	((population or founder or cultur*) adj2 (dynamic* or genetic* or effect* or group* or character* or general)).ti,ab,kf.
58	exp *jew/
59	(ethnic* or ancestr* or religio* or jew or jews or jewish or ashkenazi* or sephardi* or sefardi* or polish or poles or poland or afrikaner* or icelandic* or iceland).ti,ab,kf.
60	or/53,56-59
61	exp *mass screening/ or *early cancer diagnosis/
62	((population* or mass or cancer*) adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or diagnos* or identif* or predict*)).ti,ab,kf.
63	*germline mutation/
64	((germline* or germ line* or pathogenic) adj2 (carrier* or variant* or mutat*) adj3 (test* or analys?s or assess* or evaluat*)).ti,ab,kf.
65	exp *genetic screening/
66	(genetic adj2 (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or method*)).ti,ab,kf.
67	exp *sequence analysis/
68	((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) adj2 (sequenc* or technique* or technolog* or method* or applicat*)).ti,ab,kf.
69	((sanger or dna) adj2 (sequenc* or method* or technique* or technolog* or applicat*)).ti,ab,kf.
70	chain termination method*.ti,ab,kf.
71	((multi* adj3 probe amplification*) or MLPA).ti,ab,kf.
72	(next generation sequenc* or NGS).ti,ab,kf.
73	exp *risk assessment/ or *risk factor/
74	((risk* or probabil*) adj3 (high* or increas* or factor* or rais* or low* or reduc* or assess* or predict* or analys?s)).ti,ab,kf.
75	or/61-74
76	60 and 75
77	52 and 76
78	letter.pt. or letter/
79	note.pt.
80	editorial.pt.
81	case report/ or case study/
82	(letter or comment*).ti.
83	or/78-82
84	randomized controlled trial/ or random*.ti,ab.
85	83 not 84
86	animal/ not human/
87	nonhuman/
88	exp Animal Experiment/

#	Searches
89	exp Experimental Animal/
90	animal model/
91	exp Rodent/
92	(rat or rats or mouse or mice or rodent*).ti.
93	or/85-92
94	77 not 93
95	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
96	94 not 95
97	limit 96 to English language
98	random*.ti,ab.
99	factorial*.ti,ab.
100	(crossover* or cross over*).ti,ab.
101	((doubl* or singl*) adj blind*).ti,ab.
102	(assign* or allocat* or volunteer* or placebo*).ti,ab.
103	crossover procedure/
104	single blind procedure/
105	randomized controlled trial/
106	double blind procedure/
107	or/98-106
108	systematic review/
109	meta-analysis/
110	(meta analy* or metanaly* or metaanaly*).ti,ab.
111	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
112	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
113	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
114	(search* adj4 literature).ab.
115	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
116	((pool* or combined) adj2 (data or trials or studies or results)).ab.
117	cochrane.jw.
118	or/108-117
119	Clinical study/
120	Case control study/
121	Family study/
122	Longitudinal study/
123	Retrospective study/
124	comparative study/
125	Prospective study/
126	Randomized controlled trials/
127	125 not 126
128	Cohort analysis/
129	cohort analy$.tw.
130	(Cohort adj (study or studies)).tw.
131	(Case control$ adj (study or studies)).tw.
132	(follow up adj (study or studies)).tw.
133	(observational adj (study or studies)).tw.
134	(epidemiologic$ adj (study or studies)).tw.
135	(cross sectional adj (study or studies)).tw.
136	case series.tw.
137	prospective.tw.
138	retrospective.tw.
139	or/119-124,127-138
140	97 and (107 or 118 or 139)

1 **Database: Cochrane Database of Systematic Reviews Issue 1 of 12, January 2023 and**
2 **Cochrane Central Register of Controlled Trials Issue 1 of 12, January 2023**

3 **Date of last search: 25/01/2023**

#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Breast Neoplasms] explode all trees
#5	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#6	((breast* or mammary) NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab,kw
#7	{OR #4-#6}
#8	#3 OR #7
#9	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees
#10	MeSH descriptor: [Pedigree] this term only
#11	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees
#12	((hereditary or inherit* or familial) NEAR/3 (nonpolyposis or "non polyposis") NEAR/3 (colon or colorectal or bowel) NEAR/3 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#13	((lynch or "Muir Torre") NEAR/2 (syndrome* or cancer*)):ti,ab,kw
#14	HNPCC:ti,ab,kw
#15	(peutz* or intestin* NEXT polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* NEAR/1 lentigino*)):ti,ab,kw
#16	((hamartoma* or "polyps and spots" or cowden*) NEAR/2 (syndrome* or polyp*)):ti,ab,kw
#17	((hereditary or inherit* or familial or adenomato* or attenuated) NEAR/3 polyp* NEAR/3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)):ti,ab,kw
#18	gardner* NEXT syndrome*:ti,ab,kw
#19	(MUTYH or MYH or FAP or AFAP or APC):ti,ab,kw
#20	((familial or inherit* or heredit* or predispos* or pre NEXT dispos* or susceptib* or ancestr* or genealog* or descent) NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#21	("hereditary breast and ovarian cancer" or HBOC or "Li Fraumeni syndrome" or SBLA or LFS):ti,ab,kw
#22	(famil* NEAR/2 histor* NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#23	MeSH descriptor: [Risk Factors] this term only
#24	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais*) NEAR/3 (mutat* or malignan* or gene* or variant*)):ti,ab,kw
#25	((carrier* or gene*) NEAR/3 mutat*):ti,ab,kw
#26	MeSH descriptor: [Genes, Tumor Suppressor] explode all trees
#27	MeSH descriptor: [Tumor Suppressor Proteins] explode all trees
#28	((tumor* or tumour* or cancer* or metastasis or metastases or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#29	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#30	{OR #9-#29}
#31	#8 AND #30
#32	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#33	(("Fanconi Anemia" or "fanconi anaemia") NEAR/3 protein*):ti,ab,kw
#34	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2):ti,ab,kw
#35	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#36	MeSH descriptor: [Rad51 Recombinase] this term only
#37	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#38	(("Ataxia telangiectasia" NEAR/1 mutated NEAR/1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#39	MeSH descriptor: [Checkpoint Kinase 2] this term only

#	Searches
#40	(((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2):ti,ab,kw
#41	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]
#42	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#43	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or "SNF2 beta"):ti,ab,kw
#44	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#45	(((Sertoli or leydig) NEAR/3 (tumor* or tumour* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or androblastoma* or andreoblastoma* or SLCT or gynandroblastoma*):ti,ab,kw
#46	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H48 LIKE"):ti,ab,kw
#47	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#48	Epithelial NEXT cell NEXT adhesion NEXT molecule*:ti,ab,kw
#49	(EPCAM* or "EP CAM" or ESA or KSA or M4S1 or "MK 1" or DIAR5 or EGP* or Ly74 or gp40 or CD326 or GA733* or GA 733 or KS14 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or "MOC 31" or "Ber Ep4" or TACSTD1):ti,ab,kw
#50	{OR #32-#49}
#51	#31 OR #50
#52	MeSH descriptor: [Genetics, Population] this term only
#53	MeSH descriptor: [Founder Effect] this term only
#54	MeSH descriptor: [Cultural Characteristics] this term only
#55	MeSH descriptor: [Population Groups] explode all trees and with qualifier(s): [genetics - GE]
#56	((population or founder or cultur*) NEAR/2 (dynamic* or genetic* or effect* or group* or character* or general)):ti,ab,kw
#57	MeSH descriptor: [Jews] this term only
#58	(ethnic* or ancestr* or religio* or jew or jews or jewish or ashkenazi* or sephardi* or sefardi* or polish or poles or poland or afrikaner* or icelandic* or iceland):ti,ab,kw
#59	{OR #52-#58}
#60	MeSH descriptor: [Mass Screening] explode all trees
#61	MeSH descriptor: [Early Detection of Cancer] this term only
#62	((population* or mass or cancer*) NEAR/2 (test* or screen* or analysis or analyses or assess* or evaluat* or detect* or incidence* or diagnos* or identif* or predict*)):ti,ab,kw
#63	MeSH descriptor: [Germ-Line Mutation] this term only
#64	((germline* or germ NEXT line* or pathogenic) NEAR/2 (carrier* or variant* or mutat*) NEAR/3 (test* or analysis or analyses or assess* or evaluat*)):ti,ab,kw
#65	MeSH descriptor: [Genetic Testing] explode all trees
#66	(genetic NEAR/2 (test* or screen* or analysis or analyses or assess* or evaluat* or detect* or incidence* or method*)):ti,ab,kw
#67	MeSH descriptor: [Sequence Analysis] explode all trees
#68	(("low throughput" or "high throughput" or HTS or deep or Illumina or ion or "massively parallel" or pyro*) NEAR/2 (sequenc* or technique* or technolog* or method* or applicat*)):ti,ab,kw
#69	((sanger or dna) NEAR/2 (sequenc* or method* or technique* or technolog* or applicat*)):ti,ab,kw
#70	chain termination NEXT method*:ti,ab,kw
#71	((multi* NEAR/3 probe amplification*) or MLPA):ti,ab,kw
#72	("next generation sequence" or "next generation sequencing" or NGS):ti,ab,kw
#73	MeSH descriptor: [Risk Assessment] explode all trees
#74	MeSH descriptor: [Risk Factors] this term only
#75	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais* or low* or reduc* or assess* or predict* or analysis or analyses)):ti,ab,kw
#76	{OR #60-#75}
#77	#59 AND #76
#78	#51 and #77
#79	conference:pt or (clinicaltrials or trialsearch):so
#80	#78 NOT #79

1 Database: Epistemonikos

2 Date of last search: 25/01/2023

#	Searches
1	(advanced_title_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer)) OR advanced_abstract_en:(((ovarian OR breast) AND (familial OR hered*) AND cancer))))
2	(advanced_title_en:(((population OR founder OR cultur*) AND (dynamic* OR genetic* OR effect* OR group* OR character* OR general))) OR advanced_abstract_en:(((population OR founder OR cultur*) AND (dynamic* OR genetic* OR effect* OR group* OR character* OR general))))
3	(advanced_title_en:((ethnic* OR ancestr* OR jew OR jews OR jewish OR ashkenazi* OR sephardi* OR sefardi* OR polish OR poles OR poland OR afrikaner* OR icelandic* OR iceland)) OR advanced_abstract_en:((ethnic* OR ancestr* OR jew OR jews OR jewish OR ashkenazi* OR sephardi* OR sefardi* OR polish OR poles OR poland OR afrikaner* OR icelandic* OR iceland))))
4	2 OR 3
5	1 AND 4

3 Database: INAHTA International HTA Database

4 Date of last search: 25/01/2023

#	Searches
1	"Ovarian Neoplasms"[mhe]
2	(((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR (((ovar* AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
3	#2 OR #1
4	"Breast Neoplasms"[mhe]
5	"Neoplasms, Ductal, Lobular, and Medullary"[mh]
6	(((breast* or mammary) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[Title] OR (((breast* or mammary) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[abs]
7	#6 OR #5 OR #4
8	#7 OR #3
9	(((hereditary or inherit* or familial) AND (nonpolyposis or non polyposis) AND (colon or colorectal or bowel) AND cancer*)))[Title] OR (((hereditary or inherit* or familial) AND (nonpolyposis or non polyposis) AND (colon or colorectal or bowel) AND cancer*)))[abs]
10	((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[Title] OR ((peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1))[abs]
11	(((hereditary or inherit* or familial or adenomato* or attenuated) AND polyp* AND (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)))[Title] OR (((hereditary or inherit* or familial or adenomato* or attenuated) AND polyp* AND (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)))[abs]
12	((MUTYH or MYH or FAP or AFAP or APC))[Title] OR ((MUTYH or MYH or FAP or AFAP or APC))[abs]
13	(((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib*) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR (((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib*) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
14	(("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS))[Title] OR (("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS))[abs]
15	(((carrier* or gene*) AND mutat*))[Title] OR (((carrier* or gene*) AND mutat*))[Source]
16	#15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
17	#16 AND #8
18	((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2 or DICER1 or SMARCA4 or STK11 or LKB1 or PJS or hLKB1 or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1 or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2 or MUTYH or MYH or FAP or AFAP or APC))[Title] OR ((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2 or DICER1 or SMARCA4 or STK11 or LKB1 or PJS or hLKB1 or ATM or AT1 or ATA or ATC or ATD or ATDC

#	Searches
	or ATE or TEL1 or TELO1 or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2 or MUTYH or MYH or FAP or AFAP or APC))[abs]
19	#18 OR #17
20	(((population or founder or cultur*) AND (dynamic* or genetic* or effect* or group* or character* or general)))[Title] OR (((population or founder or cultur*) AND (dynamic* or genetic* or effect* or group* or character* or general)))[abs]
21	((ethnic* or ancestr* or religio* or jew or jews or jewish or ashkenazi* or sephardi* or sefardi* or polish or poles or poland or afrikaner* or icelandic* or iceland))[Title] OR ((ethnic* or ancestr* or religio* or jew or jews or jewish or ashkenazi* or sephardi* or sefardi* or polish or poles or poland or afrikaner* or icelandic* or iceland))[abs]
22	"Mass Screening"[mhe]
23	"Early Detection of Cancer"[mh]
24	(((population* or mass or cancer*) AND (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or diagnos* or identif* or predict*)))[Title] OR (((population* or mass or cancer*) AND (test* or screen* or analys?s or assess* or evaluat* or detect* or incidence* or diagnos* or identif* or predict*)))[abs]
25	"Germ-Line Mutation"[mh]
26	(((germline* or germ line* or pathogenic) AND (carrier* or variant* or mutat*) AND (test* or analys?s or assess* or evaluat*)))[Title] OR (((germline* or germ line* or pathogenic) AND (carrier* or variant* or mutat*) AND (test* or analys?s or assess* or evaluat*)))[abs]
27	"Genetic Testing"[mhe]
28	((genetic AND (test* or screen* or analys*s or assess* or evaluat* or detect* or incidence* or method*)))[Title] OR ((genetic AND (test* or screen* or analys*s or assess* or evaluat* or detect* or incidence* or method*)))[abs]
29	"Sequence Analysis"[mhe]
30	(((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) AND (sequenc* or technique* or technolog* or method* or applicat*)))[Title] OR (((low throughput or high throughput or HTS or deep or Illumina or ion or massively parallel or pyro*) AND (sequenc* or technique* or technolog* or method* or applicat*)))[abs]
31	(((sanger or dna) AND (sequenc* or method* or technique* or technolog* or applicat*)))[Title] OR (((sanger or dna) AND (sequenc* or method* or technique* or technolog* or applicat*)))[abs]
32	(("chain termination method*"))[Title] OR (("chain termination method*"))[abs]
33	((multi* AND probe amplification*))[Title] OR ((multi* AND probe amplification*))[abs]
34	((MLPA))[Title] OR ((MLPA))[abs]
35	(("next generation sequenc*" or NGS))[Title] OR (("next generation sequenc*" or NGS))[abs]
36	"Risk Assessment"[mhe]
37	"Risk Factors"[mh]
38	(((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[Title] OR (((risk* or probabil*) AND (high* or increas* or factor* or rais*) AND (mutat* or malignan* or gene* or variant*)))[abs]
39	#38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22
40	#21 OR #20
41	#40 AND #39
42	#41 AND #19

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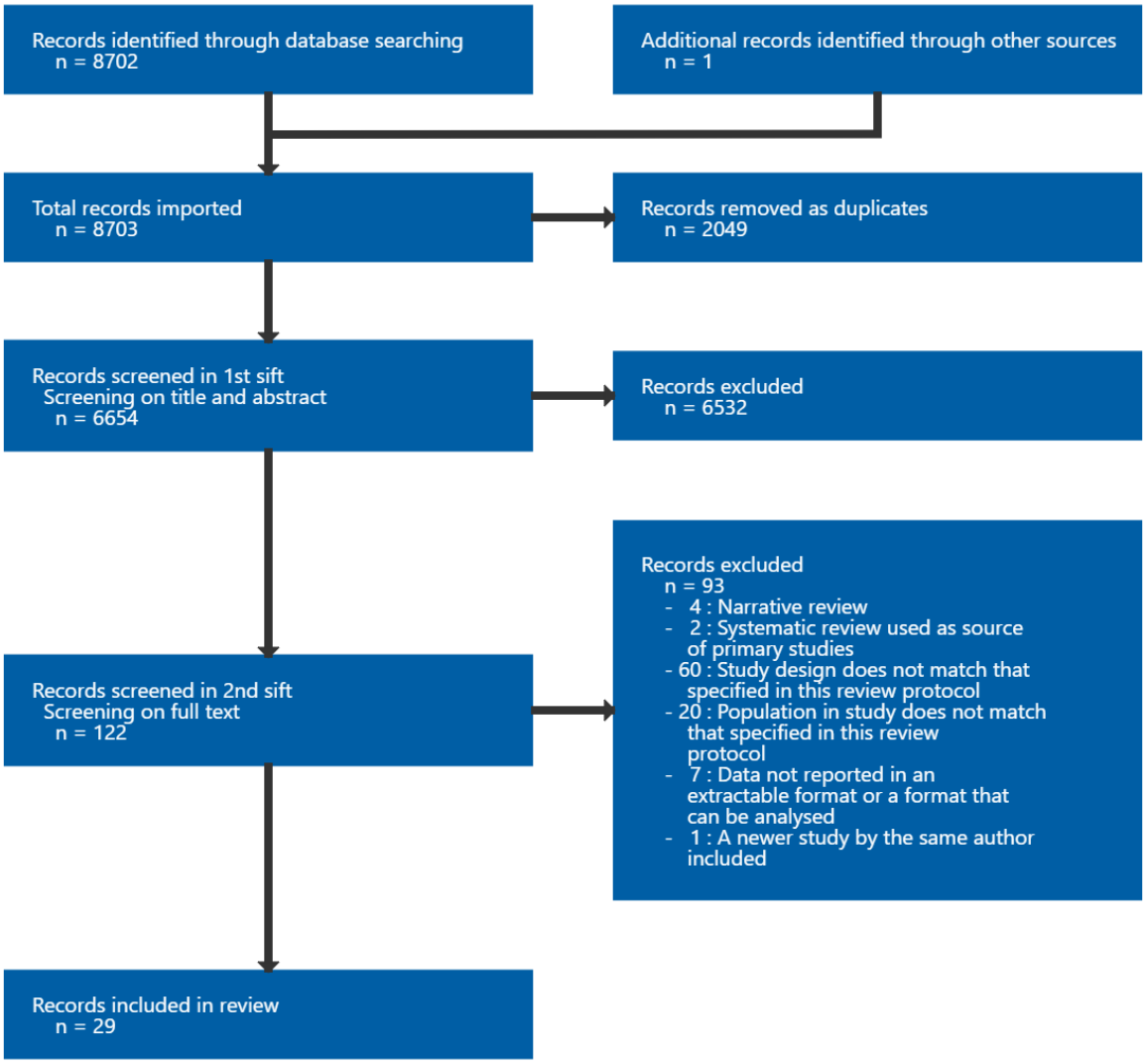
Appendix C Effectiveness evidence study selection

Study selection for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Abul-Husn, 2019

Bibliographic Reference Abul-Husn, Noura S; Soper, Emily R; Odgis, Jacqueline A; Cullina, Sinead; Bobo, Dean; Moscati, Arden; Rodriguez, Jessica E; CBIPM Genomics, Team; Regeneron Genetics, Center; Loos, Ruth J F; Cho, Judy H; Belbin, Gillian M; Suckiel, Sabrina A; Kenny, Eimear E; Exome sequencing reveals a high prevalence of BRCA1 and BRCA2 founder variants in a diverse population-based biobank.; Genome medicine; 2019; vol. 12 (no. 1); 2

Study details

Country/ies where study was carried out	The USA
Study type	Cross-sectional
Study dates	Between 2007 and 2015
Inclusion criteria	BioMe (Biobank in New York City) participants: • aged 18 years or older • with exome sequence data available
Exclusion criteria	Not reported
Population categories	African American/African in the US* Ashkenazi Jewish in the US *assumed that probably it is a mixture of East African with white European

Patient characteristics	N = 6874 African American, N = 3889 Ashkenazi Jews **Age (median (range), years):** 59 (45-70) **Gender (n):** women = 17914 (59.3%) **Ethnicity:** African American/African and Ashkenazi Jewish **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Sample preparation and exome sequencing were performed at the Regeneron Genetics Center as previously as described by Dewey et al. 2017
Sources of funding	Supported by dedicated funding to the Center for Genomic Health by the Icahn School of Medicine at Mount Sinai. E.E.K., N.S.A-H., S.A.S., J.A.O., J.E.R., and G.M.B. are supported by the National Institutes of Health, National Human Genome Research Institute (NHGRI), and National Institute on Minority Health and Health Disparities (U01 HG009610). E.E.K. is also supported by NHGRI (R01 HG010297, U01 HG009080, UM1 HG0089001, U01 HG007417); the National Heart, Lung, Blood Institute (R01 HL104608, X01 HL1345); and the National Institute of Diabetes and Kidney and Digestive Disease (R01 DK110113)

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Study arms

African American/African (N = 6874)

Ashkenazi Jewish (N = 3889)

Outcomes

***BRCA1/2* prevalence**

Outcome	African American/African, N = 6874	Ashkenazi Jewish, N = 3889
***BRCA1* (5382insC and 185delAG) / *BRCA2* (6174delT) prevalence** No of events	n = 31; % = 0.45	n = 80; % = 2.1

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes

Section	Question	Answer
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Ahearn, 2022**

Bibliographic Reference	Ahearn, TU; Pal Choudhury, P; Derkach, A; Wiafe-Addai, B; Awuah, B; Yarney, J; Edusei, L; Titiloye, N; Adjei, E; Vanderpuye, V; et, al.; Breast cancer risk in women from Ghana carrying rare germline pathogenic mutations; Cancer epidemiology, biomarkers & prevention; 2022

3 **Study details**

Country/ies where study was carried out	Ghana
Study type	Case-control The study examined the associations between pathogenic variants in women with breast cancer compared to women without breast cancer. For the present purposes the data from the control group met the inclusion criteria and were included.
Study dates	Not reported
Inclusion criteria	People: frequency matched population-based controls using census-based sampling of women between the ages of 18 to 74 years of age.
Exclusion criteria	Not reported
Population categories	Ghanaians in Ghana
Patient characteristics	N=1563 **Age (mean (SD), years):** 45.8 (12.7)

	Gender (n): women **Ethnicity (n):** Ghanaians **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	The following filters at the VCF level: Phred-scaled sequencing quality assessment of the bases contributing to the variant (QUAL) <30, allele fraction <0.2 and mean mapping quality (MQMEAN) <60, mean number of mismatches per read (NM) >2.0, AFxBase Depth <7.5. Variants failing any of these filters were removed. PTVs were defined as frameshifting insertions/ deletions, stop/gain or canonical splice variants as classified by the Emsembl Variant Effect Predictor (19), except for variants in the last exon of each gene, which were excluded from the primary analysis. Missense variants defined as pathogenic or likely pathogenic in ClinVar by two or more clinical laboratories (Ambry Genetics, SCRP, Invitae, GeneDx, Counsyl, InSiGHT) were considered pathogenic, the same criteria as applied by Palmer and colleagues in the study of AA women (Palmer 2020).
Sources of funding	The authors acknowledge the research contributions of the Cancer Genomics Research Laboratory for their expertise, execution, and support of this research in the areas of project planning, wet laboratory processing of specimens, and bioinformatics analysis of generated data. This research was supported in part by funds from the intramural research program of the NCI, NIH (to M. Garcia-Closas) and the European Union's Horizon 2020 Research and Innovation Programme (BRIDGES: grant number 634935; to D.F. Easton) and the Welcome Trust (grant no: v203477/Z/ 16/Z; to D.F. Easton). Funded with intramural funds from the NCI, NIH

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1 **Study arms**

2 **Ghanaians in Ghana (N = 1563)**

3 **Outcomes**

4 **Prevalence**

Outcome	**Ghanaians in Ghana, N = 1563**
***ATM* prevalence** No of events	n = 5; % = 0.32
***BRCA1* prevalence** No of events	n = 3; % = 0.19
***BRCA2* prevalence** No of events	n = 8; % = 0.51
***BRIP1* prevalence** No of events	n = 2; % = 0.13
***CHEK2* prevalence** No of events	n = 1; % = 0.06
***PALB2* prevalence** No of events	n = 1; % = 0.06
***MLH1* prevalence** No of events	n = 0; % = 0
***MSH2* prevalence**	n = 1; % = 0.06

Outcome	Ghanaians in Ghana, N = 1563
No of events	
***MSH6* prevalence** No of events	n = 3; % = 0.19
***RAD51C* prevalence** No of events	n = 1; % = 0.06
***RAD51D* prevalence** No of events	n = 0; % = 0
***PMS2* prevalence** No of events	n = 0; % = 0

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2 **Critical appraisal - JBI Prevalence checklist**

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes

Section	Question	Answer
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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3 **Anisimenko, 2013**

Bibliographic Reference Anisimenko, Maksim S; Mitrofanov, Dmitriy V; Chasovnikova, Olga B; Voevoda, Mikhail I; Kovalenko, Sergey P; BRCA1 gene mutations frequency estimation by allele-specific real-time PCR of pooled genomic DNA samples.; Breast (Edinburgh, Scotland); 2013; vol. 22 (no. 4); 532-6

4 **Study details**

Country/ies where study was carried out	Russia
Study type	Cross-sectional
Study dates	Not reported
Inclusion criteria	Participants in the Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) Study from Novosibirsk in Siberia (a random sample). Blood samples from 7920 donors were collected from the HAPIEE study. Approximately 97% of the Novosibirsk population is Caucasian
Exclusion criteria	Not reported
Population categories	Russians in Russia

Patient characteristics	N=7920 **Age (mean (SD), years):** 53.8 (7), range 46-69 **Gender:** not reported **Ethnicity:** Russians **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Antiprimer quenching-based real-time PCR
Sources of funding	None reported

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 7920**
***BRCA1* (185delAG, T300G, 4153delA, 5382insC)** No of events	n = 24; % = 0.3

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

Bar-Sade, 1997

Bibliographic Reference	Bar-Sade RB; Theodor L; Gak E; Kruglikova A; Hirsch-Yechezkel G; Modan B; Kuperstein G; Seligsohn U; Rechavi G; Friedman E; Could the 185delAG BRCA1 mutation be an ancient Jewish mutation? European journal of human genetics: EJHG; 1997; vol. 5 (no. 6)

Study details

Country/ies where study was carried out	Israel

Study type	Cross-sectional recruitment is unclear
Study dates	Not reported
Inclusion criteria	Iraqi-born individuals identified and recruited at the Sheba Medical Center (SMC), without preselection for history of cancer. All were volunteers unrelated to each other, interviewed with respect to family history of cancer, and their Iraqi ancestry was verified at least 2 generations back.
Exclusion criteria	Not reported
Population categories	Iraqi-Jewish population (Iraqi-born) in Israel
Patient characteristics	N=639 **Age (years, range):** 32-93 **Gender (n):** women 329 (51.5%) **Ethnicity:** those with Iraqi ancestry **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	PCR amplification of *BRCA1* exon 2 from peripheral blood DNA, was performed as described in Friedman et al. 1994; Ozelik et al. 1996; Modan et al. 1996. DNA sequencing was performed for PCR fragments that consistently displayed abnormal migration patterns on heteroduplex analysis, with the use of a biotinylated primer.
Sources of funding	Not reported

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Outcomes

***BRCA1* prevalence**

Outcome	Study, N = 639
***BRCA1* (185delAG) prevalence** No of events	n = 3; % = 0.47

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Unclear
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1 **Bar-Sade, 1998**

Bibliographic Reference Bar-Sade, RB; Kruglikova, A; Modan, B; Gak, E; Hirsh-Yechezkel, G; Theodor, L; Novikov, I; Gershoni-Baruch, R; Risel, S; Papa, MZ; Ben-Baruch, G; Friedman, E; The 185delAG BRCA1 mutation originated before the dispersion of Jews in the diaspora and is not limited to Ashkenazim.; Human molecular genetics; 1998; vol. 7 (no. 5); 801-5

2 **Study details**

Country/ies where study was carried out	Israel
Study type	Cross-sectional recruitment is unclear
Study dates	Not reported
Inclusion criteria	Individuals previously identified (no details given) and voluntarily recruited from various departments and outpatient clinics of the Sheba Medical Centre without preselection of history of cancers
Exclusion criteria	Not reported
Population categories	Non-Ashkenazi Israeli Jews of: • Moroccan origin • Yemenite origin • Iranian origin
Patient characteristics	All tested participants were unrelated to each other and their ancestry was verified at least 2 generations back. Non-Ashkenazi Israeli Jews of: • Moroccan origin: n=354 • Yemenite origin: n=200 • Iranian origin: n=150

	Age: not reported **Gender:** not reported **Ethnicity:** non-Ashkenazi Israeli Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	PCR amplified exon 2 fragments of the *BRCA1* gene were generated from DNA extracted from blood samples, using primer sequences and protocol described by Friedman et al. 1994.
Sources of funding	None reported

Study arms

Non-Ashkenazi Israeli Jews of Moroccan origin (N = 354)

Non-Ashkenazi Israeli Jews of Yemenite origin (N = 200)

Non-Ashkenazi Israeli Jews of Iranian origin (N = 150)

Outcomes

***BRCA1* (185delAG) prevalence**

Outcome	Non-Ashkenazi Israeli Jews of Moroccan origin, N = 354	Non-Ashkenazi Israeli Jews of Yemenite origin, N = 200	Non-Ashkenazi Israeli Jews of Iranian origin, N = 150
***BRCA1* (185delAG)**	n = 4; % = 1.1	n = 0; % = 0	n = 0; % = 0

Outcome	Non-Ashkenazi Israeli Jews of Moroccan origin, N = 354	Non-Ashkenazi Israeli Jews of Yemenite origin, N = 200	Non-Ashkenazi Israeli Jews of Iranian origin, N = 150
prevalence No of events			

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2 **Critical appraisal - JBI Prevalence checklist**

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Unclear
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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4 **Castillo, 2022**

Bibliographic Castillo C; Artagaveytia N; Brignoni L; Laitman Y; Camejo N; Hernández AL; Krygier G; Cayota A; Delgado L; Friedman E;

Reference Population-based screening of Uruguayan Ashkenazi Jews for recurrent BRCA1 and BRCA2 pathogenic sequence variants.; Molecular genetics & genomic medicine; 2022; vol. 10 (no. 6)

1 **Study details**

Country/ies where study was carried out	Uruguay
Study type	Cross-sectional
Study dates	Between April and November 2018
Inclusion criteria	Individuals of any gender, aged ≥25 years, with at least one of the four grandparents (maternal/ paternal) being of Ashkenazi Jewish ancestry, not previously genotyped for BRCA1 and BRCA2 pathogenic sequence variants (PSVs), and no known BRCA1/ BRCA2 PSVs in the family were eligible
Exclusion criteria	Not reported
Population categories	Ashkenazi Jews in Uruguay
Patient characteristics	N=327 **Age categories (years, n):** <40=86 (26.3%), >=40 to <60=174 (53.2%), >=60=67 (20.5%) **Gender (n):** women 312 (95.4%) **Ethnicity (n):** 4 Ashkenazi grandparents = 261 (79.8%); at least one Sephardic grandparent = 34 (10.4%), at least one non-Jewish grandparent = 11 (3.4%), at least one grandparent of unknown origin = 8 (2.5%) **Socioeconomic and geographical factors:** level of education (n): college = 250 (76.4%), high school = 63 (19.2%), primary = 1 (0.3%), no data = 13 (4%) **Disabilities:** not reported **People with communication needs:** not reported

	Non-binary people: not reported **Personal and/or family history for suggestive of inherited cancer (n)**: 82 (15%)
Germline pathogenic variant analysis	Pathogenic sequence variants identified using the array were confirmed with a new DNA sample extracted from blood, and analysis by conventional sequencing (Sanger) performed at MACROGEN (Seoul, Korea), Institut Pasteur de Montevideo, Uruguay, and Laboratorio Genia (Montevideo, Uruguay)
Sources of funding	Not reported

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 327**
***BRCA1* (185delAG) prevalence** No of events	n = 3; % = 0.92
***BRCA1* (185delAG) prevalence** Custom value	95%CI (0.31 to 2.6)

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes *(although 15% had personal/family history for suggestive of inherited cancer)*
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes

Section	Question	Answer
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Cybulski, 2019**

Bibliographic Reference Cybulski, Cezary; Kluzniak, Wojciech; Huzarski, Tomasz; Wokolorczyk, Dominika; Kashyap, Aniruddh; Rusak, Bogna; Stempa, Klaudia; Gronwald, Jacek; Szymiczek, Agata; Bagherzadeh, Maryam; Jakubowska, Anna; Debniak, Tadeusz; Lener, Marcin; Rudnicka, Helena; Szwiec, Marek; Jarkiewicz-Tretyn, Joanna; Stawicka, Malgorzata; Domagala, Pawel; Narod, Steven A; Lubinski, Jan; Akbari, Mohammad R; Polish Hereditary Breast Cancer, Consortium; The spectrum of mutations predisposing to familial breast cancer in Poland.; International journal of cancer; 2019; vol. 145 (no. 12); 3311-3320

3 **Study details**

Country/ies where study was carried out	Poland
Study type	Case-control

	The study examined the frequency of pathogenic variants in people with breast cancer compared to those without breast cancer. For the present purposes the data from the control group met the inclusion criteria and were included
Study dates	Between 2000-2017
Inclusion criteria	People: Polish cancer-free individuals (no details given)
Exclusion criteria	Not reported
Population categories	Polish people in Poland
Patient characteristics	N=2036 (cancer-free controls) **Age:** not reported **Gender:** not reported **Ethnicity:** Polish people **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Mutation analysis for the three common Polish *BRCA1* mutations was performed using PCR assay as described by Górski et al. 2005. A large deletion of exon 9 and 10 of CHEK2 gene was genotyped using multiplex-PCR reaction as described by Cybulski et al. 2007. All small mutations were genotyped using TaqMan assay (Thermo Fisher Scientific, Waltham, MA) using LightCycler® Real-Time PCR 480 System (Roche Life Science, Penzberg, Germany). All mutations were confirmed by Sanger sequencing.
Sources of funding	Not reported

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Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 4570**
***BRCA1* (c.5266dupC, c.181T>G, c.4035delA) prevalence** No of events	n = 22; % = 0.5

***CHEK2* prevalence**

Outcome	**Study, N = 4346**
***CHEK2* (c.444+1G>A, c.1100delC, del5395) prevalence** No of events	n = 3; % = 0.9

***PALB2* prevalence**

Outcome	**Study, N = 4702**
***PALB2* (c.509_510delGA, c.172_175delTTGT) prevalence** No of events	n = 10; % = 0.2

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Unclear
Questions	Was the sample size adequate?	Yes

Section	Question	Answer
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Unclear
Questions	Was the condition measured in a standard, reliable way for all participants?	Unclear
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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3 **Gabai-Kapara, 2014**

Bibliographic Reference Gabai-Kapara E; Lahad A; Kaufman B; Friedman E; Segev S; Renbaum P; Beeri R; Gal M; Grinshpun-Cohen J; Djemal K; Mandell JB; Lee MK; Beller U; Catane R; King MC; Levy-Lahad E; Population-based screening for breast and ovarian cancer risk due to BRCA1 and BRCA2.; Proceedings of the National Academy of Sciences of the United States of America; 2014; vol. 111 (no. 39)

4 **Study details**

Country/ies where study was carried out	Israel
Study type	Cross-sectional
Study dates	Between June 2004 and December 2010
Inclusion criteria	Males visiting health-related settings throughout Israel and 30 years or older, identified all 4 grandparents as Ashkenazi Jewish, no personal history of cancer. Family history of cancer was not a criterion for or against inclusion in the study.

Exclusion criteria	Not reported
Population categories	Ashkenazi Jews in Israel
Patient characteristics	N=8195 **Age:** not reported **Gender:** men **Ethnicity:** Ashkenazi Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Participants provided blood or buccal sample from which DNA was extracted and genotyped for *BRCA1* (185del AG, 5382insC) and *BRCA2* (6174delT). No other details reported.
Sources of funding	Supported by the Breast Cancer Research Foundation, the Israel National Institute for Health Policy Research, the Israel Cancer Association, and National Insitute's of Health Grant R01CA157744

1 **Outcomes**

2 ***BRCA1/2* prevalence**

Outcome	**Study, N = 8195**
***BRCA1* (185del AG, 5382insC) prevalence** includes n=3 with both BRCA1 and BRCA2 mutations No of events	n = 94; % = 1.14

Outcome	Study, N = 8195
***BRCA2* (6174delT) prevalence** includes n=3 with both BRCA1 and BRCA2 mutations No of events	n = 84; % = 1.03
***BRCA1* (185del AG, 5382insC) / BRCA2 (6174delT) prevalence** No of events	n = 178; % = 2.17

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1 **Harboe, 2009**

Bibliographic Reference	Harboe TL; Eiberg H; Kern P; Ejlertsen B; Nedergaard L; Timmermans-Wielenga V; Nielsen IM; Bisgaard ML; A high frequent BRCA1 founder mutation identified in the Greenlandic population.; Familial cancer; 2009; vol. 8 (no. 4)

2 **Study details**

Country/ies where study was carried out	Greenland
Study type	Cross-sectional
Study dates	Between 1989 and 2004
Inclusion criteria	Inhabitants from the Municipality of Ammassalik, East Greenland participating in a population-based investigation of carrier status for 2 autosomal recessive diseases (Cholestasis Familiaris Groenlandica and Propionic Acidemia)
Exclusion criteria	Not reported
Population categories	Greenlandic Inuit origin population in Greenland
Patient characteristics	N=1071 (the samples cover 36.8% of the Ammassalik population) **Age:** not reported **Gender:** not reported **Ethnicity (n):** Greenlandic Inuit population **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline	*BRCA1* p.Cys39Gly mutation genotyping was performed using allele-specific PCR amplification with mutation-specific

pathogenic variant analysis	forward primer BRCA1-39syg-F: 5'-AGGAACCTGTCTCCACAAACG-3' and reverse primer BR CA1-39-R: 5'-TCCTGGGTTATGAAGGACAAA-3'.
Sources of funding	Supported by various foundations

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 1071**
***BRCA1* (p.Cys39Gly) prevalence** No of events	n = 104; % = 9.7

***BRCA1* prevalence in Greenlandic population (pregnant women)**

Outcome	**Study, N = 1798**
***BRCA1* (p.Cys39Gly) prevalence** No of events	n = 29; % = 1.6

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No

Section	Question	Answer
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Hartge, 1999**

Bibliographic Reference	Hartge P; Struewing JP; Wacholder S; Brody LC; Tucker MA; The prevalence of common BRCA1 and BRCA2 mutations among Ashkenazi Jews.; American journal of human genetics; 1999; vol. 64 (no. 4)

3 **Study details**

Country/ies where study was carried out	The USA
Study type	Cross-sectional
Study dates	Spring 1996
Inclusion criteria	Ashkenazi Jewish men and women in the Washington, DC, area and over the age of 20
Exclusion criteria	Not reported
Population categories	Ashkenazi Jews in the US
Patient characteristics	N=5318

	Age categories (in those without caner, years (n)): 21-39=915, 40-59=2684, >=60=1363 **Gender (n):** women 3742 (70.4%) **Ethnicity:** Ashkenazi Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported **Breast cancer in participant (n):** 288 (8%) **Ovary cancer in participant (n)**: 17 **Prostate cancer in participant (n)**: 48
Germline pathogenic variant analysis	PCR-based assays were used to test DNA samples for the 185delAG and 5382insC mutations in *BRCA1* and the 6174delT mutations in *BRCA2*.
Sources of funding	Not reported

Outcomes

***BRCA1/2* prevalence**

Outcome	**Study, N = 5318**
***BRCA1* (185delAG, 5382incC)/ BRCA2 (6174delT)** No of events	n = 120; % = 2.3

Outcome	Study, N = 5318
***BRCA1* (185delAG, 5382incC)/ BRCA2 (6174delT)** Custom value	95%CI (1.9 to 2.7)

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes *(although 17% with ovarian cancer and 2.3% had cancer in the family)*
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1 **Johannesdottir, 1996**

Bibliographic Reference Johannesdottir, G; Gudmundsson, J; Bergthorsson, J T; Arason, A; Agnarsson, B A; Eiriksdottir, G; Johannsson, O T; Borg, A; Ingvarsson, S; Easton, D F; Egilsson, V; Barkardottir, R B; High prevalence of the 999del5 mutation in icelandic breast and ovarian cancer patients.; Cancer research; 1996; vol. 56 (no. 16); 3663-5

2 **Study details**

Country/ies where study was carried out	Iceland
Study type	Case-control The study examined the frequency of *BRCA2* mutation in people with breast, ovarian, prostate and other cancers compared to those without these cancers. For the present purposes the data from the control group met the inclusion criteria and were included
Study dates	1993
Inclusion criteria	People: consisted of randomly selected DNA samples from participants in the Icelandic National Diet Survey. All subjects came from the southwest part of Iceland, where well over 50% of the population lives.
Exclusion criteria	Not reported
Population categories	Icelanders in Iceland
Patient characteristics	N=499 **Age:** not reported **Gender:** not reported **Ethnicity:** Icelanders **Socioeconomic and geographical factors:** not reported

	Disabilities: not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Thermal cycling (PCR) was carried out in 25-microliter volumes containing 0.3 units Dynazyme polymerase (Finnzyme Oy), the reaction buffer provided with the polymerase. 200 micromolar of each deoxynucleotide triphosphate, 30 mg of genomic DNA, and 50 ng of each primer. Cycling conditions were 35 cycles of 95°Cfor 30 s, 55°C for 30 s and 72°Cfor 40 s.
Sources of funding	Not reported

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2 **Outcomes**

3 ***BRCA2* prevalence**

Outcome	**Study, N = 499**
***BRCA2* (999del5) prevalence** No of events	n = 2; % = 0.4

4 **Critical appraisal - JBI Prevalence checklist**

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes

Section	Question	Answer
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

Kerr, 2022

Bibliographic Reference	Kerr, S.M.; Cowan, E.; Klaric, L.; Bell, C.; O'Sullivan, D.; Buchanan, D.; Grzymski, J.J.; Center, R.G.; van Hout, C.V.; Tzoneva, G.; Shuldiner, A.R.; Wilson, J.F.; Miedzybrodzka, Z.; Clinical case study meets population cohort: Identification of a BRCA1 pathogenic founder variant in Orcadians; medRxiv; 2022

Study details

Country/ies where study was carried out	UK
Study type	Cross-sectional
Study dates	Between 2005 and 2011
Inclusion criteria	Volunteers were required to be aged 18 or over, with two or more grandparents born in Orkney
Exclusion criteria	Not reported
Population categories	Orcadians in the Northern Isles of Scotland
Patient characteristics	N=2088

	Age (median (range), years): not reported **Gender (n):** not reported **Ethnicity (n):** Orcadians **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	DNA from all ORCADES participants was used for genome-wide genotyping on the GSA BeadChip (Illumina) at the Regeneron Genetics Centre. The fully quality controlled exome sequence data set was prepared at the Regeneron Genetic Centre, following the process detailed for UK Biobank by van Hout et al. 2020
Sources of funding	Funded by the MRC University Unit award to the MRC Human Genetics Unit, University of Edinburgh, MC_UU_00007/10. LK was supported by an RCUK Innovation Fellowship from the National Productivity Investment Fund (MR/R026408/1). ORCADES was supported by the Chief Scientist Office of the Scottish Government (CZB/4/276 and CZB/4/710), a Royal Society URF to JFW and Arthritis Research UK

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 2088**
***BRCA1* (V1736A) prevalence** No of events	n = 20; % = 0.96

1 **Critical appraisal - JBI Prevalence checklist**

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

2 **Lener, 2016**

Bibliographic Reference	Lener, M.R.; Scott, R.J.; Kluzniak, W.; Baszuk, P.; Cybulski, C.; Wiechowska-Kozlowska, A.; Huzarski, T.; Byrski, T.; Kladny, J.; Pietrzak, S.; Soluch, A.; Jakubowska, A.; Lubinski, J.; Do founder mutations characteristic of some cancer sites also predispose to pancreatic cancer? International Journal of Cancer; 2016; vol. 139 (no. 3); 601-606

3 **Study details**

Country/ies where study was carried out	Poland

Study type	Case-control The study examined the frequency of 10 Polish founder mutations in people with pancreatic cancer compared to those without pancreatic cancer. For the present purposes the data from the control group met the inclusion criteria and were included
Study dates	Between 2003 and 2004
Inclusion criteria	People: 3 groups were combined. The first consisted of 2000 newborn children from 10 hospitals throughout Poland (Szczecin, Białystok, Gorzow Wielkopolski, Katowice, Wrocław, Poznan, Opole, Łodz and Rzeszow) collected between 2003 and 2004. The second group was taken from adult patient lists of three family doctors practicing in the Szczecin region. About 1000 controls were selected at random from the patient lists of these family doctors. The third group consisted of adults from Szczecin who submitted blood for paternity testing.
Exclusion criteria	Not reported
Population categories	Polish people in Poland
Patient characteristics	N=4000 **Age:** not reported **Gender:** not reported **Ethnicity:** Polish people **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	DNA was isolated from 5 to 10 mL of peripheral blood. Ten founder mutations in *BRCA1*, *CHEK2*, *NBS1* and *PALB2* genes were genotyped as described in Gorski 2005, Cybulski 2015, Cybulski 2006

Sources of funding	Not reported

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 4000**
***BRCA1* (5382insC, C61G, 4153delA) prevalence** No of events	n = 17; % = 0.42

***CHEK2* prevalence**

Outcome	**Study, N = 4000**
***CHEK2* prevalence** No of events	n = 236; % = 5.9

***PALB2* prevalence**

Outcome	**Study, N = 4000**
***PALB2* prevalence** No of events	n = 8; % = 0.2

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Unclear

Section	Question	Answer
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Lieberman, 2017**

Bibliographic Reference	Lieberman, S.; Tomer, A.; Ben-Chetrit, A.; Olsha, O.; Strano, S.; Beeri, R.; Koka, S.; Fridman, H.; Djemal, K.; Glick, I.; Zalut, T.; Segev, S.; Sklair, M.; Kaufman, B.; Lahad, A.; Raz, A.; Levy-Lahad, E.; Population screening for BRCA1/BRCA2 founder mutations in Ashkenazi Jews: Proactive recruitment compared with self-referral; Genetics in Medicine; 2017; vol. 19 (no. 7); 754-762

3 **Study details**

Country/ies where study was carried out	Israel
Study type	Cross-sectional
Study dates	Not reported

Inclusion criteria	• Ashkenazi Jews (AJ) (self-defined as four grandparents of AJ origin), • age ≥25 years, • previously unaffected with cancer, • and without a known familial BRCA mutation. Participants were not selected based on cancer family history. Recruitment: self-referral or proactive recruitment in medical settings
Exclusion criteria	Not reported
Population categories	Ashkenazi Jews in Israel
Patient characteristics	N=1771 **Age (mean (SD), years):** 52 (13) **Gender:** women 79% **Ethnicity:** Ashkenazi Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Testing for the AJ founder mutations *BRCA1*-185delAG (c.68_69delAG), *BRCA1*-5382insC (c.5266dupC), and *BRCA2*-6174delT (c.5946delT) was performed as previously published in Gabai-Kapara et al. 2014
Sources of funding	Supported by a grant from the Breast Cancer Research Foundation (NY) (to E.L.L.)

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Outcomes

***BRCA1/2* prevalence**

Outcome	Study, N = 1771
***BRCA1* (185delAG, 5382insC) / *BRCA2* (6174delT)** No of events	n = 32; % = 1.8

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1 **Manchanda, 2020**

Bibliographic Reference	Manchanda, R.; Burnell, M.; Gaba, F.; Desai, R.; Wardle, J.; Gessler, S.; Side, L.; Sanderson, S.; Loggenberg, K.; Brady, A.F.; Dorkins, H.; Wallis, Y.; Chapman, C.; Jacobs, C.; Legood, R.; Beller, U.; Tomlinson, I.; Menon, U.; Jacobs, I.; Randomised trial of population-based BRCA testing in Ashkenazi Jews: long-term outcomes; BJOG: An International Journal of Obstetrics and Gynaecology; 2020; vol. 127 (no. 3); 364-375

2 **Study details**

Country/ies where study was carried out	the UK
Study type	Randomised controlled trial (RCT) (data were analysed as observational and not as randomised data)
Study dates	Between October 2008 and July 2010
Inclusion criteria	Ashkenazi Jewish women/men >18 years old
Exclusion criteria	Known BRCA mutation, first-degree-relative of a BRCA carrier or previous BRCA testing
Population categories	Ashkenazi Jews in the UK
Patient characteristics	N=1034 **Age (mean (SD), years)*:** family history group n=54.3 (14.31), population screening group n=54.3 (14.99) **Gender:** women 66.8% **Ethnicity:** Ashkenazi Jews **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported *taken from Manchanda et al. 2015

Germline pathogenic variant analysis	Genetic testing was performed on all population screening arm volunteers and only family history (FH) arm volunteers fulfilling standard FH-based criteria
Sources of funding	Supported by 'The Eve Appeal' charity (grant number GTCV) and by researchers at the Barts Cancer Research UK Centre for Excellence, Queen Mary University of London (C16420/ A18066)

Outcomes

***BRCA1/2* prevalence**

Outcome	**Study, N = 1034**
***BRCA1* (185delAG, 5382insC) / BRCA2 (6174delT) prevalence** No of events	n = 30; % = 2.9
***BRCA1* (185delAG, 5382insC) / BRCA2 (6174delT) prevalence** Custom value	95%CI (1.97 to 4.12)

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes

Section	Question	Answer
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1

2 **Metcalfe, 2010**

Bibliographic Reference	Metcalfe KA; Poll A; Royer R; Llacuachaqui M; Tulman A; Sun P; Narod SA; Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women.; Journal of clinical oncology: official journal of the American Society of Clinical Oncology; 2010; vol. 28 (no. 3)

3 **Study details**

Country/ies where study was carried out	Canada
Study type	Cross-sectional
Study dates	May 2008
Inclusion criteria	Women who self-identified as Ashkenazi or Sephardic Jewish, were between the ages of 25 and 80 y., and lived in Ontario. Participants were not selected on the basis of family or personal history of cancer and women in these 2 categories were not excluded.
Exclusion criteria	Not reported

Population categories	Ashkenazi/Sephardic Jews in Canada
Patient characteristics	N=2080 **Age (mean (range), years):** 49.3 (24-79) **Gender:** women **Ethnicity (n):** n=1886 reported 100% Ashkenazi Jewish ancestry, n=105 women reported 75% Ashkenazi Jewish ancestry, n=56 women reported 50% Ashkenazi Jewish ancestry, n=3 women reported 25% Ashkenazi Jewish ancestry; n=17 were of Sephardic Jewish ancestry **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported **Personal history of cancer (n)**: 162 (6 with invasive breast cancer, 9 with ductal/lobular carcinoma in situ, 3 with ovarian cancer, 147 with other forms of cancer)
Germline pathogenic variant analysis	All DNA samples were tested for *BRCA1* (185delAG, 5382insC) and *BRCA2* (6174delT) mutations. The molecular technique used was done using a specific assay for Jewish mutations (Kuperstein et al. 2000).
Sources of funding	Not reported

Outcomes

***BRCA1/2* prevalence**

Outcome	**Study, N = 2080**

Outcome	Study, N = 2080
***BRCA1* (185delAG, 5382insC) prevalence** No of events	n = 10; % = 0.5
***BRCA2* (6174delT) prevalence** No of events	n = 12; % = 0.6
***BRCA1* (185delAG, 5382insC) / *BRCA2* (6174delT) prevalence** No of events	n = 22; % = 1.1

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes

Section	Question	Answer
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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3 **Noskowicz, 2014**

Bibliographic Reference Noskowicz, Monika; Bogdanova, Natalia; Bermisheva, Marina; Takhirova, Zalina; Antonenkova, Natalia; Khusnutdinova, Elza; Bremer, Michael; Christiansen, Hans; Park-Simon, Tjoung-Won; Hillemanns, Peter; Dork, Thilo; Prevalence of PALB2 mutation c.509_510delGA in unselected breast cancer patients from Central and Eastern Europe.; Familial cancer; 2014; vol. 13 (no. 2); 137-42

4 **Study details**

Country/ies where study was carried out	Byelorussia, Germany and Russia
Study type	Case-control The study examined the frequency of *PALB2* mutation in people with breast cancer compared to those without breast cancer. For the present purposes the data from the control group met the inclusion criteria and were included
Study dates	2005 in Germany, not reported for other countries
Inclusion criteria	Byelorussia people: ascertained from healthy female Byelorussian blood donors who had no personal or family history of cancer and were recruited at the Minsk centre during the same time period Germany people: taken from a cohort of healthy female German blood donors recruited in 2005 at the same university hospital

	Russia people: healthy volunteers from the same geographic regions of which patients were tested
Exclusion criteria	Not reported
Population categories	Byelorussians in Byelorussia Germans in Germany Russians in Russia
Patient characteristics	N=1242 in Byelorussia N=989 in Germany N=596 in Russia **Age:** not reported **Gender:** not reported **Ethnicity:** Byelorussians, Germans and Russians **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Genomic DNA was isolated from peripheral white blood cells by routine phenol–chloroform extraction. High resolution melting analysis of PCR amplicons from the *PALB2* exon 4 that harbours the c.509_510delGA mutation, was performed on a Rotor-Gene 6000 real-time PCR machine (Corbett Research, Mortlake, Australia) as described in Bogdanova 2011.
Sources of funding	One author was supported by an intramural Hannelore-Munke fellowship at Hannover Medical School. The Hannover laboratory was furthermore supported by the Rudolf Bartling Foundation.

Study arms

Byelorussians in Byelorussia (N = 1242)

Germans in Germany (N = 989)

Russians in Russia (N = 596)

Outcomes

***PALB2* prevalence**

Outcome	Byelorussians in Byelorussia, N = 1242	Germans in Germany, N =	Russians in Russia, N = 596
***PALB2* (c.509_510delGA) prevalence** No of events	n = 0; % = 0	n = 0; % = 0	n = 0; % = 0

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Unclear
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes

Section	Question	Answer
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Pavlovica, 2022**

Bibliographic Reference Pavlovica, K.; Irmejs, A.; Noukas, M.; Palover, M.; Kals, M.; Tonisson, N.; Metspalu, A.; Gronwald, J.; Lubinski, J.; Murmane, D.; Kalnina, A.; Loza, P.; Maksimenko, J.; Trofimovics, G.; Subatniece, S.; Daneberga, Z.; Miklasevics, E.; Gardovskis, J.; Spectrum and frequency of CHEK2 variants in breast cancer affected and general population in the Baltic states region, initial results and literature review; European Journal of Medical Genetics; 2022; vol. 65 (no. 5); 104477

3 **Study details**

Country/ies where study was carried out	Estonia
Study type	Cross-sectional
Study dates	Not reported
Inclusion criteria	Participants in the Estonian Biobank (EstBB) which is a population-based biobank of the Institute of Genomics at the University of Tartu
Exclusion criteria	Not reported
Population categories	Estonians in Estonia
Patient characteristics	N=4776

	Age (mean (range), years): 49.3 (24-79) **Gender:** women 47% **Ethnicity:** Estonians **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Whole-genome (N-2420) and whole-exome (N-2356) sequencing
Sources of funding	Supported by the European Union through European Regional Development Fund (project No. 2014-, 2020.4.01.15–0012 GENTRANSMED), Estonian Research Council (PUT PRG555 to NT, PUTJD817 to MK, RITA1/01-42-03)

Outcomes

***CHECK2* prevalence**

Outcome	**Study, N = 4776**
***CHECK2* (c.470T > C) prevalence** No of events	n = 410; % = 8.6
***CHECK2* (c.444+1G>A) prevalence** No of events	n = 8; % = 0.2

Outcome	Study, N = 4776
***CHECK2* (c.1100delC) prevalence** No of events	n = 27; % = 0.6
***CHECK2* (c.470T > C, c.444+1G>A and c.1100delC) prevalence** No of events	n = 445; % = 9.3

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1 **Pelttari, 2012**

Bibliographic Reference Pelttari, Liisa M; Kiiski, Johanna; Nurminen, Riikka; Kallioniemi, Anne; Schleutker, Johanna; Gylfe, Alexandra; Aaltonen, Lauri A; Leminen, Arto; Heikkila, Paivi; Blomqvist, Carl; Butzow, Ralf; Aittomaki, Kristiina; Nevanlinna, Heli; A Finnish founder mutation in RAD51D: analysis in breast, ovarian, prostate, and colorectal cancer.; Journal of medical genetics; 2012; vol. 49 (no. 7); 429-32

2 **Study details**

Country/ies where study was carried out	Finland
Study type	Case-control The study examined *RAD51D* and *RAD54L* for mutations in people with breast, ovarian, colorectal, and prostate cancer compared to those without these cancers. For the present purposes the data from the control group met the inclusion criteria and were included
Study dates	Not reported
Inclusion criteria	People: healthy population controls from the Tampere region of Finland
Exclusion criteria	Not reported
Population categories	Finns in Finland
Patient characteristics	N=2102 **Age:** not reported **Gender:** not reported **Ethnicity:** Finns **Socioeconomic and geographical factors:** not reported

	Disabilities: not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	The RAD51D c.576+1G>A mutation was genotyped with Taqman real-time PCR.
Sources of funding	Supported by the Helsinki University Central Hospital Research Fund, the Academy of Finland (132473), the Sigrid Juselius Foundation, and the Finnish Cancer Society

Outcomes

***RAD51D* prevalence**

Outcome	**Study, N = 2102**
***RAD51D* (c.576+1G>A) prevalence** No of events	n = 1; % = 0.05

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No

Section	Question	Answer
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1

2 **Quintana-Murci, 2005**

Bibliographic Reference	Quintana-Murci, L.; Gal, I.; Bakhan, T.; Quach, H.; Sayar, S.H.; Shiri-Sverdlov, R.; Baruch, R.G.; McElreavey, K.; Dagan, E.; Narod, S.; Friedman, E.; The Tyr978X BRCA1 mutation: Occurrence in non-Jewish Iranians and haplotype in French-Canadian and non-Ashkenazi Jews; Familial Cancer; 2005; vol. 4 (no. 2); 85-88

3 **Study details**

Country/ies where study was carried out	Israel
Study type	Cross-sectional
Study dates	Not reported
Inclusion criteria	Iranian men unselected for personal or familial history of cancer
Exclusion criteria	Not reported
Population categories	Iranian non-Jews in Israel

Patient characteristics	N=442 **Age:** not reported **Gender:** men **Ethnicity:** Iranian non-Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Detection of the Tyr978X *BRCA1* mutation was carried out by employing modified restriction enzyme digestion and using primer sequences, cycling profile and PCR conditions to amplify the appropriate genomic DNA fragment, as previously described by Shiri-Sverdlov et al. 2001
Sources of funding	Sponsored in part by a grant from the Middle East Cancer Consortium (MECC) to Eitan Friedman

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 442**
***BRCA1* (Tyr978X) prevalence** No of events	n = 0; % = 0

1 **Critical appraisal - JBI Prevalence checklist**

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Unclear
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

2

3 **Roa, 1996**

Bibliographic Reference	Roa, BB; Boyd, AA; Volcik, K; Richards, CS; Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2.; Nature genetics; 1996; vol. 14 (no. 2); 185-7

4 **Study details**

Country/ies where study was carried out	Israel, the USA
Study type	Cross-sectional

Study dates	Not reported
Inclusion criteria	Ashkenazi Jews unselected for a personal or family history of breast/ ovarian cancer, and who previously participated in population screening for common diseases among Ashkenazi Jews including Fanconi anaemia, Tay Sachs, Canavan and Gaucher diseases
Exclusion criteria	Not reported
Population categories	• Ashkenazi Jews in Israel • Ashkenazi Jews in the US
Patient characteristics	Ashkenazi Jews in Israel: N = between 398 and 403* Ashkenazi Jews in the USA: N = between 2687 and 2717* * sample size differs for different *BRCA1* mutations tested **Age:** not reported **Gender:** not reported **Ethnicity:** Ashkenazi Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Mutation screening was performed by allele-specific oligonucleotide analysis for a panel of 5 recurrent *BRCA1* mutations and the 6174delT mutation in *BRCA2*.
Sources of funding	Not reported

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1 **Study arms**

2 **Ashkenazi Jews in Israel (N = 403)**

3 **Ashkenazi Jews in the USA (N = 2705)**

4 **Outcomes**

5 ***BRCA1* prevalence**

Outcome	Ashkenazi Jews in Israel, N = 403	Ashkenazi Jews in the US, N = 2705
***BRCA1* (185delAG) prevalence** No of events	n = 3; % = 0.74	n = 31; % = 1.15
***BRCA1* (185delAG) prevalence** Custom value	95%CI (0.15 to 2.17)	95%CI (0.78 to 1.63)
***BRCA1* (5382insC) prevalence** n differs from the above: 399 and 2717, respectively No of events	n = 0; % = 0	n = 4; % = 0.15
***BRCA1* (5382insC) prevalence** n differs from the above: 399 and 2717, respectively Custom value	95%CI (0.00 to 0.92)	95%CI (0.04 to 0.38)

6 ***BRCA2* prevalence**

Outcome	Ashkenazi Jews in Israel, N = 398	Ashkenazi Jews in the US, N = 2687
***BRCA2* (6174delT) prevalence** No of events	n = 10; % = 2.51	n = 37; % = 1.38

Outcome	Ashkenazi Jews in Israel, N = 398	Ashkenazi Jews in the US, N = 2687
***BRCA2* (6174delT) prevalence** Custom value	CI95% (1.20 to 4.62)	CI95% (0.97 to 1.90)

1

2 **Critical appraisal - JBI Prevalence checklist**

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

3

4 **Shiri-Sverdlov, 2001**

Bibliographic Reference	Shiri-Sverdlov R; Gershoni-Baruch R; Ichezkel-Hirsch G; Gotlieb WH; Bruchim Bar-Sade R; Chetrit A; Rizel S; Modan B; Friedman E; The Tyr978X BRCA1 Mutation in Non-Ashkenazi Jews: Occurrence in High-Risk Families, General Population

and Unselected Ovarian Cancer Patients.; Community genetics; 2001; vol. 4 (no. 1)

1 **Study details**

Country/ies where study was carried out	Israel
Study type	Cross-sectional recruitment is unclear
Study dates	Not reported
Inclusion criteria	Iraqi-Jewish population recruited through various departments and outpatient clinics of the Sheba Medical Center without preselection for history of cancer
Exclusion criteria	Not reported
Population categories	Iraqi Jews in Israel
Patient characteristics	N=289 **Age:** not reported **Gender:** women 66.8% **Ethnicity:** Iraqi Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline	Detection of Tyr978X *BRCA1* mutation was carried out by employing the modified restriction enzyme digest, using the

pathogenic variant analysis	primer sequences, cycling profile and PCR conditions, to amplify the appropriate genomic DNA fragment.
Sources of funding	Sponsored in part by a grant from the Israel Center Research Fund and the Middle East Cancer Consortium to Eitan Friedman

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 289**
***BRCA1* (Tyr978X) prevalence** No of events	n = 3; % = 1

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Unclear
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes

Section	Question	Answer
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Struewing, 1995**

Bibliographic Reference	Struewing JP; Abeliovich D; Peretz T; Avishai N; Kaback MM; Collins FS; Brody LC; The carrier frequency of the BRCA1 185delAG mutation is approximately 1 percent in Ashkenazi Jewish individuals.; Nature genetics; 1995; vol. 11 (no. 2)

3 **Study details**

Country/ies where study was carried out	Israel, the USA
Study type	Cross-sectional recruitment is unclear
Study dates	Not reported
Inclusion criteria	Ashkenazi Jews unselected for the presence of breast cancer or positive family history of cancer; samples were originally collected as part of genetic screening for cystic fibrosis and Tay Sachs disease
Exclusion criteria	Not reported
Population categories	Ashkenazi Jews in Israel and the US
Patient characteristics	N=858 **Age:** not reported

	Gender: not reported **Ethnicity:** non-Ashkenazi Israeli Jews **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	The presence of the mutations was determined using ASO hybridizations, as described by Struewing et al. 1995, with slight modifications.
Sources of funding	Not reported

Outcomes

***BRCA1* prevalence**

Outcome	**Study, N = 858**
***BRCA1* (185delAG) prevalence** No of events	n = 8; % = 0.9
***BRCA1* (185delAG) prevalence** Custom value	95%CI (0.4 to 0.9)

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Unclear
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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3 **Teodorczyk, 2013**

Bibliographic Reference	Teodorczyk, Urszula; Cybulski, Cezary; Wokolorczyk, Dominika; Jakubowska, Anna; Starzynska, Teresa; Lawniczak, Malgorzata; Domagala, Pawel; Ferenc, Katarzyna; Marlicz, Krzysztof; Banaszkiewicz, Zbigniew; Wisniowski, Rafal; Narod, Steven A; Lubinski, Jan; The risk of gastric cancer in carriers of CHEK2 mutations.; Familial cancer; 2013; vol. 12 (no. 3); 473-8

4 **Study details**

Country/ies where study was carried	Poland

out	
Study type	Case-control The study examined 4 Polish founder mutations in the *CHEK2* gene in people with gastric cancer compared to those without gastric cancer. For the present purposes the data from the control group met the inclusion criteria and were included
Study dates	Not reported
Inclusion criteria	People: cancer-free adults from the Polish population
Exclusion criteria	Not reported
Population categories	Polish people in Poland
Patient characteristics	N=8302 **Age (mean (SD), years):** men 61.2 (23-90), women 52.2 (19-91) **Gender:** women 52% **Ethnicity:** Polish people in Poland **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	The *CHEK2* del5395 mutation was detected by a multiplex polymerase chain reaction (PCR). The IVS2+1G>A and I157T variants were detected by restriction fragment length polymorphism PCR (RFLP-PCR) analysis, and the 1100delC mutation was analysed using an allele specific oligonucleotide (ASO) PCR assay.
Sources of funding	Not reported

Outcomes

***CHEK2* prevalence**

Outcome	Study, N = 8302
***CHEK2* ()1100delC, IVS2?1G[A and del5395 prevalence** No of events	n = 480; % = 5.8

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1 **Thorlacius, 1997**

Bibliographic Reference	Thorlacius, S.; Sigurdsson, S.; Bjarnadottir, H.; Olafsdottir, G.; Jonasson, J.G.; Tryggvadottir, L.; Tulinius, H.; Eyfjord, J.E.; Study of a single BRCA2 mutation with high carrier frequency in a small population; American Journal of Human Genetics; 1997; vol. 60 (no. 5); 1079-1084

2 **Study details**

Country/ies where study was carried out	Iceland
Study type	Cross-sectional
Study dates	Not reported
Inclusion criteria	Samples (randomly selected) from individuals were from 2 population-based screening programs, one set of samples kept at the Biological Specimen Bank of the Icelandic Cancer Society and the other from the Genetics Laboratory of the National Hospital Blood Bank; unselected for sex and family history of cancer
Exclusion criteria	Not reported
Population categories	Icelanders in Iceland
Patient characteristics	N=520 **Age:** not reported **Gender:** not reported **Ethnicity:** Icelanders **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported

	Non-binary people: not reported
Germline pathogenic variant analysis	Exon 9 fragments were PCR amplified from genomic DNA by use of primers as described by Tavtigian et al. 1996
Sources of funding	Supported by grants from the Icelandic Cancer Society Science Fund, from the University of Iceland Science Fund, and from Nordisk Cancer Union

Outcomes

***BRCA2* prevalence**

Outcome	**Study, N = 520**
***BRCA2* (999del5) prevalence** No of events	n = 3; % = 0.6

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes

Section	Question	Answer
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Tiller, 2022**

Bibliographic Reference Tiller JM; Cousens NE; Kaur R; Rowley S; Ko Y; Mahale S; Bankier A; Meiser B; Barlow-Stewart K; Burnett L; Jacobs C; James P; Trainer A; Neil S; Campbell IG; Andrews L; Delatycki M; Population-based BRCA1/2 testing programmes are highly acceptable in the Jewish community: results of the JeneScreen Study; Journal of Medical Genetics; 2022; (no. Published Online First: 03 June 2022. doi: 10.1136/jmedgenet-2022-108519)

3 **Study details**

Country/ies where study was carried out	Australia
Study type	Cross-sectional
Study dates	Not reported
Inclusion criteria	• Age ≥18 years old • Has at least one Jewish grandparent (does not have to be Ashkenazi Jewsih) • Currently resides in Sydney or Melbourne • Can read and communicate in English* *from Cousens 2021
Exclusion criteria	• Has previously undergone BRCA1/2 testing • Is aware of a family member who has been identified as having a BRCA1/2 mutation • Has been diagnosed with cancer within 12 months prior to participating in the study (other than non-melanoma skin

	cancer)* *from Cousens 2021
Population categories	Jews in Australia
Patient characteristics	N=2167 (tested, overall N=2274) Jews in Australia of which 94.5% Ashkenazi, 7.8% Sephardic **Age (mean (SD), years):** 48 (14) **Gender:** women 25.3% **Ethnicity:** Ashkenazi and Sephardic Jews **Socioeconomic and geographical factors (n):** education: - year 10 or below: 50 (2.2%) - year 12/TAFE certificate/diploma: 430 (19%) - university undergraduate/higher degree: 1784 (78.8%) **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	The DNA from the buccal swabs is extracted with the proteinase K DNA extraction method, followed by batch testing with high resolution melting (HRM) method to detect any variants in the targeted sequence. The results of any samples identified to have a B-JFM by HRM are validated by Sanger sequencing* *from Cousens 2021
Sources of funding	Supported by numerous philanthropic donations from individuals and organisations within the Sydney and Melbourne Jewish communities. One author supported by a fellowship.

Outcomes

***BRCA1/2* prevalence**

Outcome	Study, N = 2167
***BRCA1* (c.68_69delAG, c.5266dupC) / *BRCA2* (c.5946delT) prevalence** No of events	n = 28; % = 1.3

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

1 **Trottier, 2016**

Bibliographic Reference Trottier, M; Lunn, J; Butler, R; Curling, D; Turnquest, T; Francis, W; Halliday, D; Royer, R; Zhang, S; Li, S; Thompson, I; Donenberg, T; Hurley, J; Akbari, MR; Narod, SA; Prevalence of founder mutations in the BRCA1 and BRCA2 genes among unaffected women from the Bahamas.; Clinical genetics; 2016; vol. 89 (no. 3); 328-31

2 **Study details**

Country/ies where study was carried out	the Bahamas
Study type	Cross-sectional
Study dates	2007
Inclusion criteria	Bahamian women self-selected for inclusion and without a family history of breast or ovarian cancer, and only those who reported having at least one parent of Bahamian ancestry
Exclusion criteria	Not reported
Population categories	Bahamians in Bahamas
Patient characteristics	N=1089 **Age:** not reported **Gender:** women **Ethnicity:** Bahamian women in Bahamas **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported

Germline pathogenic variant analysis	Each mutation was genotyped by sequencing an overlapping DNA fragment using a BigDye Terminator v3.1 Cycle Sequencing Kit (Life Technologies Burlington, Ontario, Canada) on the ABI prism 3500XL Genetic Analyzer (Life Technologies Burlington, Ontario, Canada)
Sources of funding	Supported by the Bahamas Breast Cancer Initiative Foundation and by the Komen grant SG09-00001

Outcomes

***BRCA1/2* prevalence**

Outcome	**Study, N = 1089**
***BRCA1* (IVS13+1G > A, 4730insG, T5443G, IVS16+6 T>C, 185delAG, 943ins10) / *BRCA2* (8128delA) prevalence** No of events	n = 1; % = 0.09

Critical appraisal - JBI Prevalence checklist

Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes

Section	Question	Answer
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

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2 **Wokolorczyk, 2020**

Bibliographic Reference Wokolorczyk, Dominika; Kluzniak, Wojciech; Huzarski, Tomasz; Gronwald, Jacek; Szymiczek, Agata; Rusak, Bogna; Stempa, Klaudia; Gliniewicz, Katarzyna; Kashyap, Aniruddh; Morawska, Sylwia; Debniak, Tadeusz; Jakubowska, Anna; Szwiec, Marek; Domagala, Pawel; Lubinski, Jan; Narod, Steven A; Akbari, Mohammad R; Cybulski, Cezary; Polish Hereditary Prostate Cancer, Consortium; Mutations in ATM, NBN and BRCA2 predispose to aggressive prostate cancer in Poland.; International journal of cancer; 2020; vol. 147 (no. 10); 2793-2800

3 **Study details**

Country/ies where study was carried out	Poland
Study type	Case-control The study examined the frequency of pathogenic mutations in prostate susceptibility genes in men with familial prostate cancer compared to cancer-free controls. For the present purposes the data from the control group met the inclusion criteria and were included
Study dates	Between 2007 and 2012
Inclusion criteria	People selected randomly from a registry of people who participated in the population-based study, based on the following criteria: cancer-free, females at age 40 or above, males at age 45 or above, and reported negative cancer family history in first-degree relative. They were part of a population-based study of 1.5 million residents of West Pomerania, which was designed to identify family cancer clusters.
Exclusion criteria	Not reported
Population	Polish people in Poland

categories	
Patient characteristics	N=308 **Age (mean (range), years):** women: 56.9 (40-84); men: 62.1 (45-89) **Gender:** women 52% **Ethnicity:** Polish people **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Tested by exome sequencing. The Agilent SureSelect human exome kit (V6) was used for capturing sequence target regions.
Sources of funding	Funded by National Science Centre, Poland with project number: 2015/19/B/NZ2/02439

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2 **Outcomes**

3 ***ATM* prevalence**

Outcome	**Study, N = 308**
***ATM* prevalence** No of events	n = 0; % = 0

1 ***BRCA1/2* prevalence**

Outcome	Study, N = 308
***BRCA1* prevalence** No of events	n = 1; % = 0.3
***BRCA2* prevalence** No of events	n = 0; % = 0

2 ***CHEK2* prevalence**

Outcome	Study, N = 308
***CHEK2* prevalence** No of events	n = 13; % = 4.2

3 ***MSH2* prevalence**

Outcome	Study, N = 308
***MSH2* prevalence** No of events	n = 0; % = 0

4 ***MSH6* prevalence**

Outcome	Study, N = 308
***MSH6* prevalence** No of events	n = 0; % = 0

5

6

Critical appraisal - JBI Prevalence checklist

Section	Question	Answer
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	Yes
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

Zhang, 2022

Bibliographic Reference	Zhang, L.; Qin, Z.; Huang, T.; Tam, B.; Ruan, Y.; Guo, M.; Wu, X.; Li, J.; Zhao, B.; Chian, J.S.; Wang, X.; Wang, L.; Wang, S.M.; Prevalence and spectrum of DNA mismatch repair gene variation in the general Chinese population; Journal of Medical Genetics; 2022; vol. 59 (no. 7); 652-661

Study details

Country/ies where study was carried out	China, Macau, Singapore

Study type	Cross-sectional
Study dates	Not reported
Inclusion criteria	Those participating in ChinaMAP project, Singapore SG10 project, Chinese Academy of Sciences Precision Medicine Initiative project, Han Chinese study, Chinese breast cancer study (healthy controls) and Macau Chinese study conducted by the authors
Exclusion criteria	Not reported
Population categories	Ethnic Chinese population in China, Macau and Singapore
Patient characteristics	N=18844 of which 61.8% mainland Chinese, 23.6% Macau Chinese, 14.6% Singapore Chinese **Age:** not reported **Gender:** not reported **Ethnicity:** ethnic Chinese **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs:** not reported **Non-binary people:** not reported
Germline pathogenic variant analysis	Whole genome sequencing
Sources of funding	Funded by Macau Science and Technology Development Fund (085/2017/A2, 0077/2019/AMJ), University of Macau (SRG2017-00097-FHS, MYRG2019-00018-FHS), Faculty of Health Sciences, University of Macau (FHSIG/ SW/0007/2020P, Startup fund) (SMW).

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1 **Outcomes**

2 **Mismatch repair variants prevalence**

Outcome	**Study, N = 18844**
***MLH1, MSH2/6, PMS2* prevalence** No of events	n = 33; % = 0.18

3 **Critical appraisal - JBI Prevalence checklist**

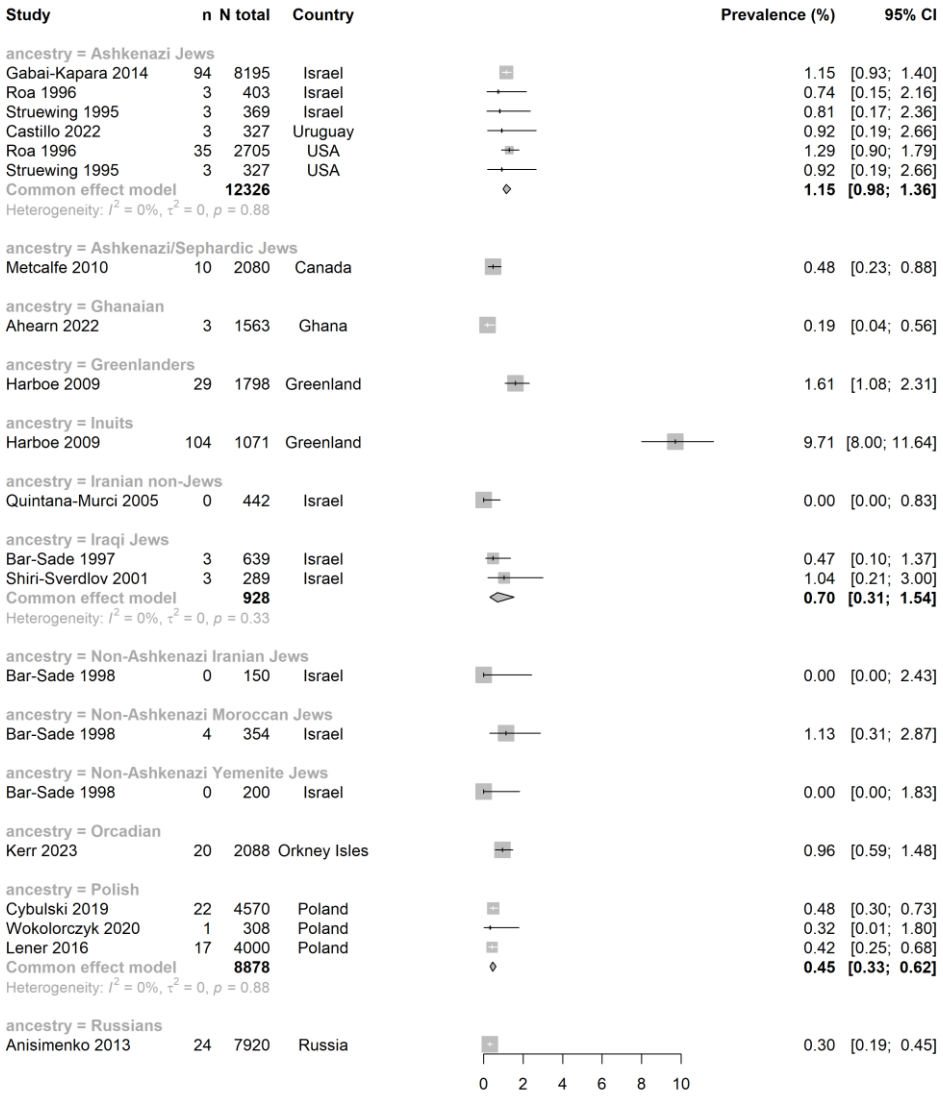
Section	**Question**	**Answer**
Questions	Was the sample frame appropriate to address the target population?	Yes
Questions	Were study participants sampled in an appropriate way?	Yes
Questions	Was the sample size adequate?	Yes
Questions	Were the study subjects and the setting described in detail?	No
Questions	Was the data analysis conducted with sufficient coverage of the identified sample?	Yes
Questions	Were valid methods used for the identification of the condition?	Yes
Questions	Was the condition measured in a standard, reliable way for all participants?	Yes
Questions	Was there appropriate statistical analysis?	Yes
Questions	Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes

Appendix E Forest plots

Forest plots for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

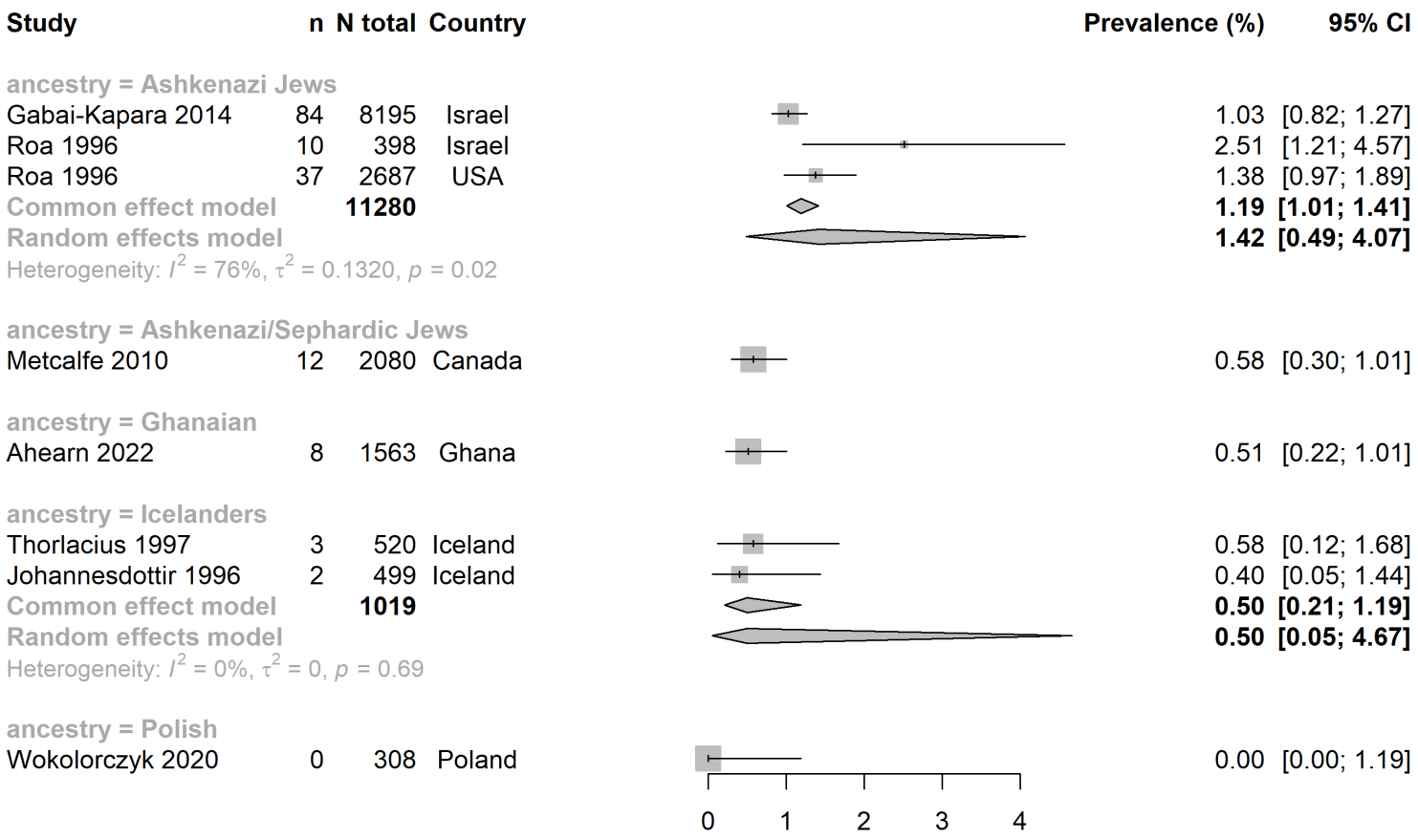
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Prevalence of pathogenic *BRCA1* variants according to ancestry



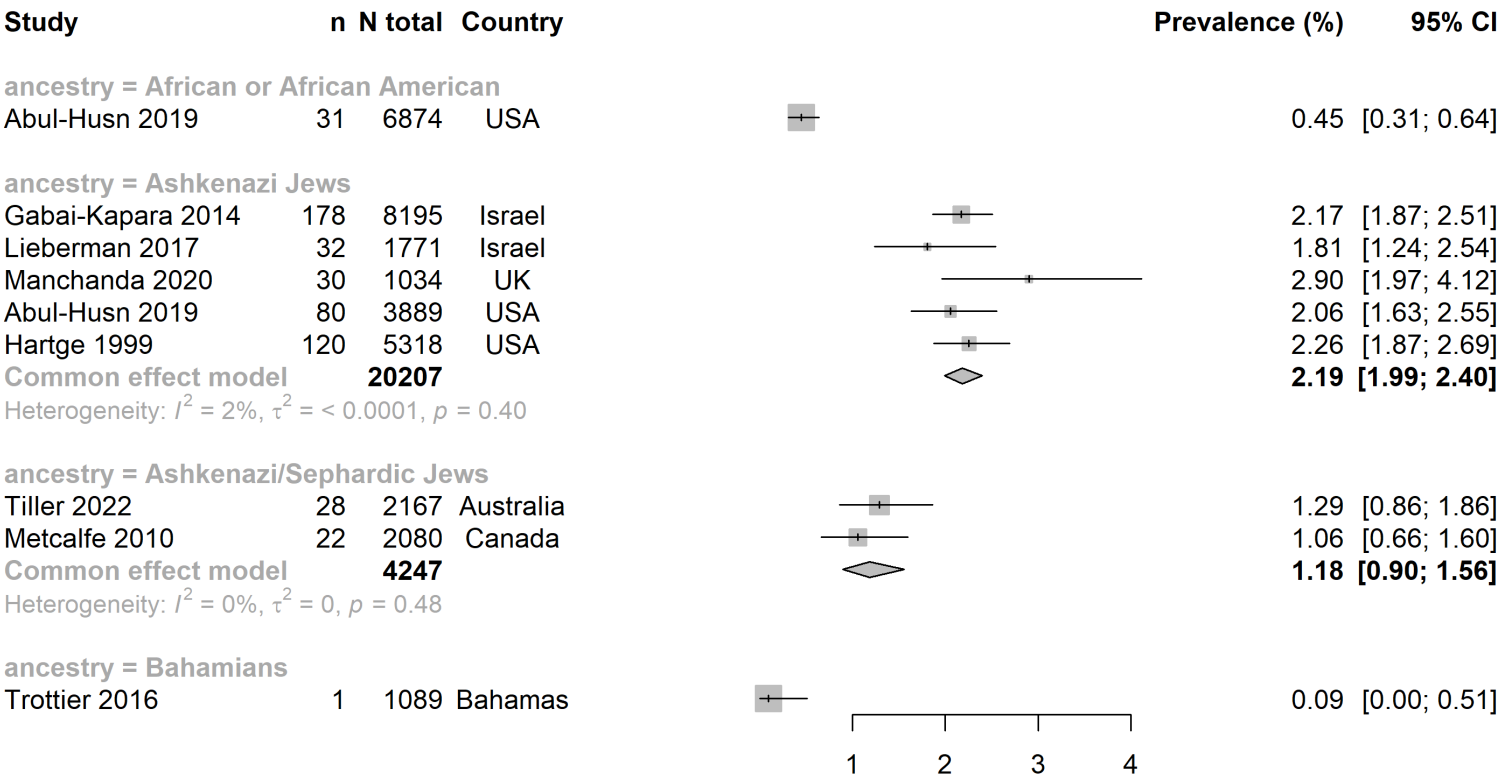
CI: confidence interval

Figure 3: Prevalence of pathogenic *BRCA2* variants according to ancestry



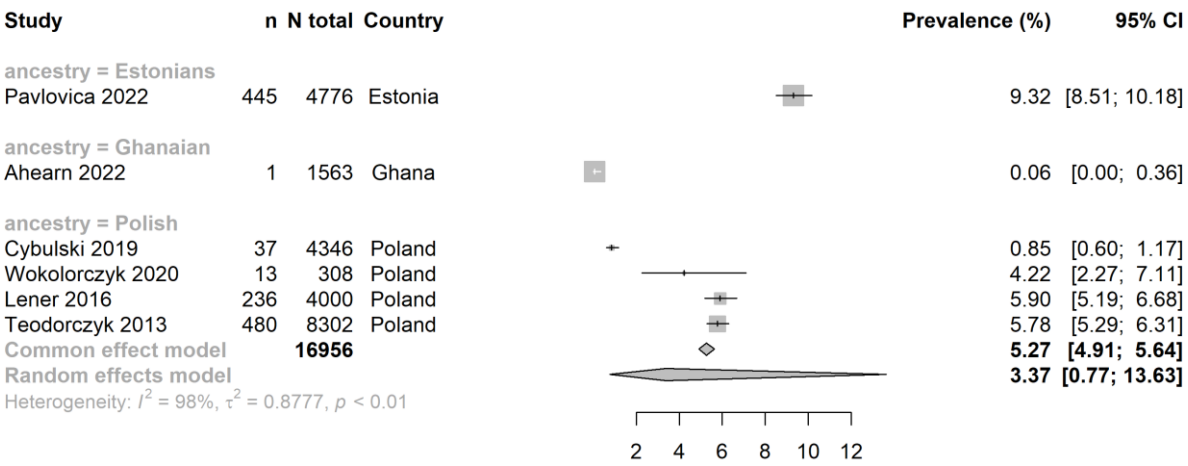
CI: confidence interval

Figure 4: Prevalence of pathogenic *BRCA1* or *BRCA2* variants according to ancestry



CI: confidence interval

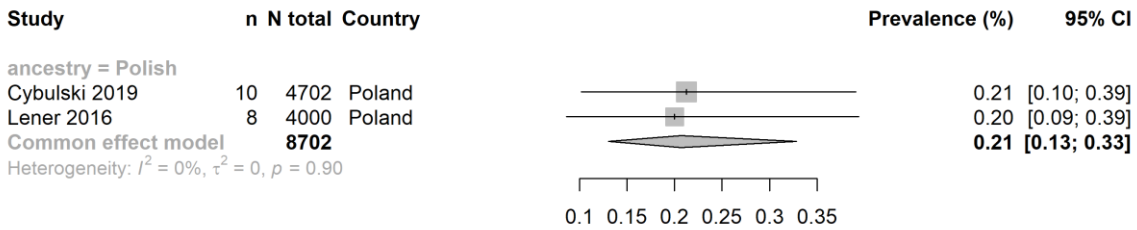
Figure 5: Prevalence of pathogenic *CHEK2* variants according to ancestry



CI: confidence interval; RE: random effects

1

Figure 6: Prevalence of pathogenic *PALB2* variants in Polish people



CI: confidence interval

Appendix F GRADE tables

GRADE tables for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Table 5: Evidence profile for prevalence of *ATM* in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Prevalence of *ATM* pathogenic variants in Polish people in Poland								
Wokolorczyk 2020	Case-control	0/308	0.00% [0.00% to 1.30%]	Not serious	Not serious	Not serious	Serious[1]	Moderate
Prevalence of *ATM* pathogenic variants in Ghanaian people in Ghana								
Ahearn 2022	Case-control	5/1563	0.32% [0.14% to 0.75%]	Not serious	Not serious	Not serious	Not serious	High

CI: confidence interval
1 Sample size 200-400

Table 6: Evidence profile for prevalence of *BRCA1* pathogenic variants in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *BRCA1* pathogenic variants in Ashkenazi Jewish people in Israel, the USA and Uruguay									
4[1]	Cross-sectional	141/12326	1.15% [0.93% to 1.40%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of BRCA1 pathogenic variants in Ashkenazi / Sephardic Jewish people in Canada									
Metcalfe 2010	Cross-sectional	10/2080	0.48% [0.23% to 0.88%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Ghanaian people in Ghana									
Ahearn 2022	Case-control	3/1563	0.19% [0.04% to 0.56%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Greenlandic population (pregnant women) in Greenland									

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Harboe 2009	Cross-sectional	29/1798	1.61% [1.08% to 2.31%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Greenlandic Inuit origin population in Greenland									
Harboe 2009	Cross-sectional	104/1071	9.71% [8.00% to 11.64%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Iranian non-Jewish people in Israel									
Quintata-Murci 2005	Cross-sectional	0/442	0.00% [0.00% to 0.83%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Iraqi Jewish people in Israel									
2[3]	Cross-sectional	6/928	0.70% [0.31% to 1.54%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *BRCA1* pathogenic variants in non-Ashkenazi Jewish people of Iranian origin in Israel									
Bar-Sade 1998	Cross-sectional	0/150	0.00% [0.00% to 2.43%]	Serious[2]	Not serious	Not serious	Very serious[4]	Very low	CRITICAL
Prevalence of *BRCA1* pathogenic variants in non-Ashkenazi Jewish people of Moroccan origin in Israel									
Bar-Sade 1998	Cross-sectional	4/354	1.13% [0.31% to 2.87%]	Serious[2]	Not serious	Not serious	Serious[5]	Low	CRITICAL
Prevalence of *BRCA1* pathogenic variants in non-Ashkenazi Jewish people of Yemenite origin in Israel									
Bar-Sade 1998	Cross-sectional	0/200	0.00% [0.00% to 1.83%]	Serious[2]	Not serious	Not serious	Serious[5]	Low	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Orcadians in the Northern Isles of Scotland, UK									
Kerr 2023	Cross-sectional	20/2088	0.96% [0.59% to 1.48%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Polish people in Poland									

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
3[6]	Case-control (control arm data used)	40/8878	0.45% [0.33% to 0.62%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *BRCA1* pathogenic variants in Russians in Russia									
Anisimenko 2013	Cross-sectional	24/7920	0.30% [0.19% to 0.45%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL

CI: confidence interval
1 Gabai-Kapara 2014, Roa 1996, Struewing 1995, Castillo 2022, ,
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI prevalence checklist
3 Bar-Sade 1997, Shiri-Sverdlov 2001
4 Sample size < 200
5 Sample size 200-400
6 Cybulski 2019, Wokolorczyk 2020, Lener 2016

Table 7: Evidence profile for prevalence of *BRCA2* pathogenic variants in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *BRCA2* pathogenic variants in Ashkenazi Jewish people in Israel and the USA									
2[1]	Cross-sectional	131/11280	1.42% [0.49% to 4.07%]	Serious[2]	Serious[3]	Not serious	Not serious	Low	CRITICAL
Prevalence of *BRCA2* pathogenic variants in Ashkenazi / Sephardic Jewish people in Canada									
Metcalfe 2010	Cross-sectional	12/2080	0.58% [0.30% to 1.01%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA2* pathogenic variants in Ghanaian people in Ghana									
Ahearn 2022	Case-control	8/1563	0.51% [0.22% to 1.01%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA2* pathogenic variants in Icelanders in Iceland									

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
2[4]	Cross-sectional/ case-control	5/1019	0.50% [0.05% to 4.67%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *BRCA2* pathogenic variants in Polish people in Poland									
Wokolorczyk 2020	Case-control	0/308	0.00% [0.00% to 1.19%]	Not serious	Not serious	Not serious	Serious[5]	Moderate	CRITICAL

CI: confidence interval
1 Gabai-Kapara 2014, Roa 1996
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI prevalence checklist
3 Serious heterogeneity unexplained by subgroup analysis
4 Thorlacius 1997, Johannesdottir 1996
5 Sample size 200-400

Table 8: Evidence profile for prevalence of *BRCA1* or *BRCA2* pathogenic variants in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *BRCA1/2* pathogenic variants in African American or African people in the USA									
Abul-Husn 2019	Cross-sectional	31/6874	0.45% [0.31% to 0.64%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA1/2* pathogenic variants in Ashkenazi Jewish people in Israel, the UK and the USA									
5[1]	Cross-sectional/RCT	440/20207	2.19% [1.99% to 2.40%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA1/2* pathogenic variants in Ashkenazi / Sephardic Jewish people in Australia or Canada									
2[2]	Cross-sectional	50/4247	1.18% [0.90% to 1.56%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *BRCA1/2* pathogenic variants in Bahamians in the Bahamas									
Trottier 2016	Cross-sectional	1/1089	0.09% [0.00% to 0.51%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL

CI: confidence interval; RCT: randomised controlled trial

1 Gabai-Kapara 2014, Lieberman 2017, Manchanda 2020, Abul-Husn 2019, Hartge 1999 ,
2 Tiller 2022, Metcalfe 2010

Table 9: Evidence profile for prevalence of *BRIP1* pathogenic variants in Ghanaian population

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *BRIP1* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	2/1563	0.13% [0.04% to 0.47%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL

CI: confidence interval

Table 10: Evidence profile for prevalence of *CHEK2* pathogenic variants in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *CHECK2* pathogenic variants in Estonians in Estonia									
Pavlovica 2022	Cross-sectional	445/4776	9.32% [8.51% to 10.18%]	Serious[1]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *CHECK2* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	1/1563	0.06% [0.00% to 0.36%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *CHECK2* pathogenic variants in Polish people in Poland									
4[2]	Case-control	766/16956	3.37% (0.77% to 13.63%)	Serious[1]	Very serious[3]	Not serious	Not serious	Very low	CRITICAL

CI: confidence interval
1 Serious risk of bias in the evidence contributing to the outcomes as per JBI prevalence checklist
2 Cybulski 2019, Wokolorczyk 2020, Lener 2016, Teodorczyk 2013
3 Very serious heterogeneity unexplained by subgroup analysis

Table 11: Evidence profile for prevalence of *PALB2* pathogenic variants in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *PALB2* pathogenic variants in Polish people in Poland									
2[1]	Case-control	18/8702	0.21% [0.13% to 0.33%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *PALB2* pathogenic variants in Byelorussians in Byelorussia									
Noskowicz 2014	Case-control	0/1242	0.00% [0.00% to 0.30%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *PALB2* pathogenic variants in Germans in Germany									
Noskowicz 2014	Case-control	0/989	0.00% [0.00% to 0.40%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *PALB2* pathogenic variants in Russians in Russia									
Noskowicz 2014	Case-control	0/596	0.00% [0.00% to 0.70%]	Serious[2]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *PALB2* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	1/1563	0.06% [0.01% to 0.35%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL

CI: confidence interval
1 Cybulski 2019, Lener 2016
2 Serious risk of bias in the evidence contributing to the outcomes as per JBI prevalence checklist

Table 12: Evidence profile for prevalence of *MLH1, MSH2, MSH6 or PMS2* pathogenic variants in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *MLH1, MSH2/6 or PMS2* pathogenic variants in ethnic Chinese people in China, Macau and Singapore									
Zhang 2022	Cross-sectional	33/18844	0.20% [0.19% to 0.20%]	Serious[1]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *MSH2* pathogenic variants in Polish people in Poland									

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Wokolorczyk 2020	Case-control	0/308	0.00% [0.00% to 1.30%]	Not serious	Not serious	Not serious	Serious[2]	Moderate	CRITICAL
Prevalence of *MSH6* pathogenic variants in Polish people in Poland									
Wokolorczyk 2020	Case-control	0/308	0.00% [0.00% to 1.30%]	Not serious	Not serious	Not serious	Serious[2]	Moderate	CRITICAL
Prevalence of *MLH1* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	0/1563	0.00% [0.00% to 0.30%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *MSH2* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	1/1563	0.06% [0.01% to 0.35%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *MSH6* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	3/1563	0.19% [0.06% to 0.56%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL
Prevalence of *PMS2* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	0/1563	0.00% [0.00% to 0.002%][2]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL

CI: confidence interval
[1] Serious risk of bias in the evidence contributing to the outcomes as per JBI prevalence checklist
[2] Sample size 200-400

Table 13: Evidence profile for prevalence of *RAD51C* in Ghanaian population

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *RAD51C* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	1/1563	0.06% [0.01% to 0.35%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL

CI: confidence interval

Table 14: Evidence profile for prevalence of *RAD51D* in different populations

No. of studies	Study design	No of people with variant / No of people	Prevalence (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality	Importance
Prevalence of *RAD51D* pathogenic variants in Finns in Finland									
Pelttari 2012	Case-control	1/2102	0.05% [0.00% to 0.30%]	Serious[1]	Not serious	Not serious	Not serious	Moderate	CRITICAL
Prevalence of *RAD51D* pathogenic variants in Ghanaians in Ghana									
Ahearn 2022	Case-control	0/1563	0.00% [0.00% to 0.30%]	Not serious	Not serious	Not serious	Not serious	High	CRITICAL

CI: confidence interval

[1] *Serious risk of bias in the evidence contributing to the outcomes as per JBI prevalence checklist*

Appendix G Economic evidence study selection

Study selection for: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

One global search was undertaken – please see Supplement 2 for details on study selection.

Appendix H Economic evidence tables

Economic evidence tables for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Table 3: Economic evidence tables for *BRCA1/BRAC2* genetic testing for Jewish people unaffected by cancer

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Patel 2018 UK Cost-utility analysis Source of funding: The Eve Appeal charity	Intervention Population BRCA testing of all adult Sephardi Jewish women Comparator Clinical criteria/family history-based BRCA testing (personal history of ovarian cancer (OC) at any age, first-degree relative with OC (any age), first-degree relative with or personal history of breast cancer (BC) aged <50 years, or a first-degree relative with or personal history of male breast cancer at any age.	Sephardi Jewish women aged ≥30 years Modelling study (Markov) Source of baseline data: Penetrance rates from meta-analysis, population-based studies/ statistics Source of effectiveness data: Published studies, including cohort studies and meta-analyses Source of cost data: Published studies and NICE guidelines. Source of unit cost data: National sources (PSSRU unit costs of Health and Social Care, NHS reference costs) and published studies.	Costs: Genetic testing and counselling with DVD, risk-reducing surgery, cancer diagnosis and treatment, terminal care, breast screening, coronary heart disease Mean discounted cost per participant: Intervention: £1,714.61 Control: £1,647.53 Difference: £67.04 The primary measure of outcome: QALYs Mean discounted QALYs per participant: Intervention: 23.4226 Control: 22.4220 Difference: 1.0006	ICERs: £67.04/QALY Probability of being cost-effective: 100% at the £20k/QALY Subgroup analysis: NR Sensitivity analysis: -The model was most sensitive to BRCA1 mutation prevalence estimates in the Sephardi population and family-history-positive individuals. However, the conclusions were unchanged and ICER remained below £20k/QALY gained. - The conclusions were unchanged in scenario analyses where no benefit in breast cancer	Perspective: NHS Currency: UK£ Cost year: 2015 prices Time horizon: Lifetime (extending to 83 years) Discounting: 3.5% for costs and QALYs Applicability: Directly Limitations: Minor Other comments: - The results for the US were: $308.42/QALY, 100% at the $100k/QALY

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				risk reduction from undergoing a risk-reducing oophorectomy was modelled, no HRT was offered or a lower risk-reducing mastectomy rate of 13% (base case: 0.60) and risk-reducing oophorectomy rate of 49% (base-case: 0.66) was modelled.	
Manchanda 2017 UK Cost-utility analysis Source of funding: The Eve Appeal charity	Intervention BRCA testing for women with varying degrees of Ashkenazi Jewish (AJ) ancestry ranging from four to one AJ grandparent. Comparator Testing using family history-based clinical criteria (personal history of ovarian cancer, first-degree relative with ovarian cancer, first-degree relative with or personal history of breast cancer <50 years, first-degree relative with or personal history of male breast cancer (any age).	AJ women ≥30 years with four to one AJ grandparents. Modelling study (Decision-analytical model) Source of baseline data: Population-based studies, cohort studies including meta-analysis for penetrance Source of effectiveness data: Cohort studies, including meta-analysis Source of cost data: RCT, NICE guidelines, published studies	Costs: Genetic testing and counselling, risk-reducing surgery, cancer diagnosis and treatment, terminal care, breast screening Mean discounted cost per participant: Four AJ grandparents Intervention: £1,861 Control: £1,955 Difference: -£94 Three AJ grandparents Intervention: £1,813 Control: £1,875 Difference: -£62	ICERs: BRCA testing is dominant in AJ women with four to two AJ grandparents and cost-effective in women with one grandparent with an ICER of £863/QALY gained Probability of being cost-effective: For populations with four, three, two or one AJ grandparent(s) ≥95% at the £20k/QALY Subgroup analysis: NR Sensitivity analysis:	Perspective: NHS Currency: UK£ Cost year: 2014 prices Time horizon: Lifetime (extending till the age of 83 years) Discounting: 3.5% for costs and QALYs Applicability: Directly Limitations: Minor Other comments: The analysis was also undertaken from the US perspective. The results showed that BRCA screening was dominant in AJ women with four to one AJ grandparent. The probability of being cost-effective was ≥95% at the willingness to pay

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Source of unit cost data: National sources (PSSRU Unit costs of Health and Social Care, NHS Reference costs) and published studies	Two AJ grandparents Intervention: £1,766 Control: £1,792 Difference: -£26 One AJ grandparents Intervention: £1,718 Control: £1,705 Difference: £13 The primary measure of outcome: QALYs Four AJ grandparents Mean discounted QALYs per participant: Intervention: 23.15 Control: 23.12 Difference: 0.032 Three AJ grandparents Intervention: 23.16 Control: 23.13 Difference: 0.027 Two AJ grandparents Intervention: 23.16 Control: 23.14 Difference: 0.021	The conclusions remained unchanged in scenario analyses where no benefit with premenopausal oophorectomy on reduction in breast cancer risk (base case: 0.49) was modelled, a lower risk-reducing mastectomy rate of 13% (base case: 0.52) as reported in Israeli women was used or assuming 20% risk-reducing surgery uptake (base case: oophorectomy=0.55, mastectomy=0.52).	of $100k/QALY.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			One AJ grandparents Intervention: 23.17 Control: 23.15 Difference: 0.015		
Manchanda 2015 UK Cost-utility analysis Source of funding: The Eve Appeal charity	Intervention Population BRCA testing for AJ women Comparator Family history-based criteria for BRCA (≥10% mutation risk)	AJ women aged ≥30 years Modelling study (Decision analytic model) Source of baseline data: Penetrance from a meta-analysis of various published studies, survival from a population-based study Source of effectiveness data: Cohort studies and meta-analysis for risk-reducing surgery Source of cost data: Published studies, including RCT (GCaPPS), NICE guidelines, and published sources. Source of unit cost data: National sources	Costs: Genetic testing, counselling, risks reducing surgery, cancer diagnosis and treatment, terminal cancer, breast cancer screening Mean discounted cost per participant: Intervention: £1,677 Control: £1,741 Difference: -£64 The primary measure of outcome: QALYs Mean outcome per participant: Intervention: 23.1406 Control: 23.1096 Difference: 0.031	ICERs: Testing all AJ women for BRCA was dominant Probability of being cost-effective: 94% at £20k/QALY gained Subgroup analysis: NA Sensitivity analysis: - The conclusions were robust to changes in utility values, costs, penetrance estimates and rate of uptake of preventive/risk-reducing surgery - The model was highly sensitive to the overall BRCA prevalence and BRCA prevalence in FH-negative women. However, the conclusions remained unchanged, and the intervention remained either dominant or resulted in an ICER <	Perspective: NHS Currency: UK£ Cost year: 2010 prices Time horizon: Lifetime Discounting: 3.5% for costs and QALYs Applicability: Directly Limitations: Minor Other comments: None

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		(PSSRU unit costs of Health and social care, NHS reference costs, published sources)		£20k/QALY gained. - Modelling breast cancer prophylaxis with SERMs (tamoxifen/raloxifene) in BRCA carriers, the intervention remained dominant. - Conclusions were unchanged in a scenario where women opt for genetic testing at age 50 (average age of menopause) with a median age for risk-reducing oophorectomy and risk-reducing mastectomy at 54 years (just below the weighted average age of ovarian cancer onset in BRCA1/2 carriers).	
Michaelson-Cohen 2022 Israel Cost-utility analysis Source of funding: The Israel National Institute	Intervention BRCA testing all Ashkenazi Jewish (AJ) people (PS) Testing AJ people who meet family history criteria (has a probability of at least 10% for identifying a BRCA variant), IFH Cascade testing, which	AJ women aged 30 Modelling study (Decision tree) Source of baseline data: Published sources including registry data, population-based screening study Source of effectiveness	Costs: Written information pre-testing and post-test in-person counselling, test cost, pre-test counselling (in all AJ testing arm only), surveillance (aged 30-75: annual MRI, mammography, clinical breast exam, and biannual pelvic ultrasound, blood CA-	ICERs: -$45,333/QALY (PS vs IFH) -CT dominated (higher cost, lower QALYs) Probability of being cost-effective: 0.50 at $45k/QALY WTP and approaching 0.90 at $100k/QALY WTP	Perspective: Payer perspective Currency: US dollars Cost year: 2019 Time horizon: Unclear (seem lifetime) Discounting: 3% for costs, QALYs discounted (rate unclear) Applicability: Partially

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
for Health Policy Research grant and the Breast Cancer Research Foundation grant.	involves testing first- and second-degree relatives of known carriers, has a probability of at least 25% for identifying a BRCA variant (CT)	data: Published meta-analyses of observational studies Source of resource use data: State-mandated health service provider (Clalit Health Services) Source of unit cost data: National (Ministry of Health price list)	125), risk reducing surgery, cancer costs Mean lifetime costs per participant: PS: £$26,924 IFH: $26,652 CT: $26,991 Difference: $272 (PS vs IFH), $67 (CT vs PS) Primary measure of outcome: QALYs (utility scores from various published sources) Mean lifetime QALYs per participant: PS: 26.408 IFH: 26.402 CT: 26.386 Difference: 0.006 (PS vs IFH), -0.022 (CT vs PS)	Subgroup analysis: NR Sensitivity analysis: The ICER of PS (vs IFH) was sensitive to the carrier prevalence in AJ population and testing rates (resulted in ICERs > $200k/QALY). Also sensitive to BC reduction post RRBSO, OC risk in carriers and OC risk reduction post RRBSO with ICERs approaching $100k/QALY.	Limitations: Potentially serious Other comments: - Presentation of incremental analysis unclear making the interpretation of sensitivity analyses difficult - Included genetic testing uptake rates in an index population

Abbreviations: AJ: Ashkenazi Jewish; BC: Breast cancer; CT: Cascade testing; HRT: Hormone replacement therapy; ICER: Incremental cost-effectiveness ratio; k: Thousand; NHS: National Health Service; MRI: Magnetic resonance imaging; NICE: The National Institute for Health and Care Excellence; NR: Not reported; OC: Ovarian cancer; PS: Population screening; IFH: International family criteria; PSSRU: Personal Social Services Research Unit; QALY: Quality-adjusted life-years; RCT: Randomised controlled trial; RRBSO: Risk reducing bilateral salpingo-oophorectomy; SERM: Selective Estrogen Receptor Modulators; UK: United Kingdom; US: United States; WTP: Willingness-to-pay

Appendix I Economic model

Economic model for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

Excluded effectiveness studies

Table 15: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Alemar, B., Herzog, J., Brinckmann Oliveira Netto, C. et al. (2016) Prevalence of Hispanic BRCA1 and BRCA2 mutations among hereditary breast and ovarian cancer patients from Brazil reveals differences among Latin American populations. Cancer Genetics 209(9): 417-422	- Population in study does not match that specified in this review protocol
Astiazaran-Symonds, E., Kim, J., Haley, J.S. et al. (2022) A Genome-First Approach to Estimate Prevalence of Germline Pathogenic Variants and Risk of Pancreatic Cancer in Select Cancer Susceptibility Genes. Cancers 14(13): 3257	- Data not reported in an extractable format or a format that can be analysed
Bahar, A Y, Taylor, P J, Andrews, L et al. (2001) The frequency of founder mutations in the BRCA1, BRCA2, and APC genes in Australian Ashkenazi Jews: implications for the generality of U.S. population data. Cancer 92(2): 440-5	- Population in study does not match that specified in this review protocol
Behl, Supriya, Hamel, Nancy, de Ladurantaye, Manon et al. (2020) Founder BRCA1/BRCA2/PALB2 pathogenic variants in French-Canadian breast cancer cases and controls. Scientific reports 10(1): 6491	- Study design does not match that specified in this review protocol
Bisgin, A, Boga, I, Yalav, O et al. (2019) BRCA mutation characteristics in a series of index cases of breast cancer selected independent of family history. The breast journal 25(5): 1029-1033	- Population in study does not match that specified in this review protocol
Bjorge, T., Lie, A.K., Hovig, E. et al. (2004) BRCA1 mutations in ovarian cancer and borderline tumours in Norway: A nested case-control study. British Journal of Cancer 91(10): 1829-1834	- Study design does not match that specified in this review protocol
Bogdanova, N., Togo, A.V., Ratajska, M. et al. (2015) Prevalence of the BLM nonsense mutation, p.Q548X, in ovarian cancer patients from Central and Eastern Europe. Familial Cancer 14(1): 145-149	- Study design does not match that specified in this review protocol
Bretsky, P., Haiman, C.A., Gilad, S. et al. (2003) The relationship between twenty missense ATM variants and breast cancer risk: The multiethnic cohort. Cancer Epidemiology Biomarkers and Prevention 12(8): 733-738	- Study design does not match that specified in this review protocol
Casolino, R., Paiella, S., Azzolina, D. et al. (2021) Homologous Recombination Deficiency in Pancreatic Cancer: A Systematic Review and Prevalence Meta-Analysis. Journal of Clinical Oncology 39(23): 2617-2631	- Population in study does not match that specified in this review protocol

Study	Reason for exclusion
CHEK2 Breast Cancer Case-Control, Consortium (2004) CHEK2*1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. American journal of human genetics 74(6): 1175-82	- Study design does not match that specified in this review protocol
Ciuro, J., Beyer, A., Fritzler, J. et al. (2021) Health Care Disparities and Demand for Expanding Hereditary Breast Cancer Screening Guidelines in African Americans. Clinical Breast Cancer 21(3): e220-e227	- Population in study does not match that specified in this review protocol
Claus, E.B.; Stowe, M.; Carter, D. (2003) Family history of breast and ovarian cancer and the risk of breast carcinoma in situ. Breast Cancer Research and Treatment 78(1): 7-15	- Study design does not match that specified in this review protocol
Cybulski, C, Gorski, B, Huzarski, T et al. (2009) Effect of CHEK2 missense variant I157T on the risk of breast cancer in carriers of other CHEK2 or BRCA1 mutations. Journal of medical genetics 46(2): 132-5	- Study design does not match that specified in this review protocol
Dansonka-Mieszkowska, Agnieszka, Kluska, Anna, Moes, Joanna et al. (2010) A novel germline PALB2 deletion in Polish breast and ovarian cancer patients. BMC medical genetics 11: 20	- Study design does not match that specified in this review protocol
Dutil, Julie, Golubeva, Volha A, Pacheco-Torres, Alba L et al. (2015) The spectrum of BRCA1 and BRCA2 alleles in Latin America and the Caribbean: a clinical perspective. Breast cancer research and treatment 154(3): 441-53	- Narrative review
Esai Selvan, Myvizhi, Zauderer, Marjorie G, Rudin, Charles M et al. (2020) Inherited Rare, Deleterious Variants in ATM Increase Lung Adenocarcinoma Risk. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 15(12): 1871-1879	- Study design does not match that specified in this review protocol
Felix, G.E.S., Guindalini, R.S.C., Zheng, Y. et al. (2022) Mutational spectrum of breast cancer susceptibility genes among women ascertained in a cancer risk clinic in Northeast Brazil. Breast Cancer Research and Treatment 193(2): 485-494	- Study design does not match that specified in this review protocol
Ferla, R, Calo, V, Cascio, S et al. (2007) Founder mutations in BRCA1 and BRCA2 genes. Annals of oncology: official journal of the European Society for Medical Oncology 18suppl6: vi93-8	- Systematic review used as source of primary studies
FitzGerald, M G, Bean, J M, Hegde, S R et al. (1997) Heterozygous ATM mutations do not contribute to early onset of breast cancer. Nature genetics 15(3): 307-10	- Study design does not match that specified in this review protocol
Foglietta, J, Ludovini, V, Bianconi, F et al. (2020) Prevalence and Spectrum of BRCA Germline Variants in Central Italian High Risk or Familial Breast/Ovarian Cancer Patients: A Monocentric Study. Genes 11(8)	- Study design does not match that specified in this review protocol
Frey, M.K., Kopparam, R.V., Ni Zhou, Z. et al. (2019) Prevalence of nonfounder BRCA1/2 mutations in Ashkenazi Jewish patients presenting for genetic testing	- Population in study does not match that specified in this review protocol

Study	Reason for exclusion
at a hereditary breast and ovarian cancer center. Cancer 125(5): 690-697	
Gal, Inabr, Kimmel, Gad, Gershoni-Baruch, Ruth et al. (2006) A specific RAD51 haplotype increases breast cancer risk in Jewish non-Ashkenazi high-risk women. European journal of cancer (Oxford, England: 1990) 42(8): 1129-34	- Study design does not match that specified in this review protocol
Gifoni, A.C.L.V.C., Gifoni, M.A.C., Wotroba, C.M. et al. (2022) Hereditary Breast Cancer in the Brazilian State of Ceara (The CHANCE Cohort): Higher-Than-Expected Prevalence of Recurrent Germline Pathogenic Variants. Frontiers in Oncology 12: 932957	- Population in study does not match that specified in this review protocol
Girard, Elodie, Eon-Marchais, Severine, Olaso, Robert et al. (2019) Familial breast cancer and DNA repair genes: Insights into known and novel susceptibility genes from the GENESIS study, and implications for multigene panel testing. International journal of cancer 144(8): 1962-1974	- Study design does not match that specified in this review protocol
Goldgar, David E, Healey, Sue, Dowty, James G et al. (2011) Rare variants in the ATM gene and risk of breast cancer. Breast cancer research: BCR 13(4): r73	- Study design does not match that specified in this review protocol
Gomaa Mogahed, Salwa H, Hamed, Yasser S, Ibrahim Moursy, Yassmin E et al. (2020) Analysis of Heterozygous BRCA1 5382ins Founder Mutation in a Cohort of Egyptian Breast Cancer Female Patients Using Pyrosequencing Technique. Asian Pacific journal of cancer prevention: APJCP 21(2): 431-438	- Study design does not match that specified in this review protocol
Grana, B., Fachal, L., Darder, E. et al. (2011) Germline ATM mutational analysis in BRCA1/BRCA2 negative hereditary breast cancer families by MALDI-TOF mass spectrometry. Breast Cancer Research and Treatment 128(2): 573-579	- Study design does not match that specified in this review protocol
Gronwald, J, Huzarski, T, Byrski, T et al. (2006) Direct-to-patient BRCA1 testing: the Twoj Styl experience. Breast cancer research and treatment 100(3): 239-45	- Population in study does not match that specified in this review protocol
Hall, Michael J, Reid, Julia E, Burbidge, Lynn A et al. (2009) BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. Cancer 115(10): 2222-33	- Population in study does not match that specified in this review protocol
Hansen TV, Ejlertsen B, Albrechtsen A et al. (2009) A common Greenlandic Inuit BRCA1 RING domain founder mutation. Breast cancer research and treatment 115(1): 69-76	- Population in study does not match that specified in this review protocol
Hartge, P., Chatterjee, N., Wacholder, S. et al. (2002) Breast cancer risk in Ashkenazi BRCA1/2 mutation carriers: Effects of reproductive history. Epidemiology 13(3): 255-261	- Data not reported in an extractable format or a format that can be analysed
Hedau, Suresh, Jain, Neeraj, Husain, Syed A et al. (2004) Novel germline mutations in breast cancer susceptibility genes BRCA1, BRCA2 and p53 gene in breast cancer patients from India. Breast cancer research and treatment 88(2): 177-86	- Study design does not match that specified in this review protocol

Study	Reason for exclusion
Heise, M., Jarzemski, P., Nowak, D. et al. (2022) Clinical Significance of Gene Mutations and Polymorphic Variants and their Association with Prostate Cancer Risk in Polish Men. Cancer Control 29	- Study design does not match that specified in this review protocol
Hilz, P., Heinrihsone, R., Patzold, L.A. et al. (2019) Allelic variants of breast cancer susceptibility genes PALB2 and RECQL in the Latvian population. Hereditary Cancer in Clinical Practice 17(1): 17	- Study design does not match that specified in this review protocol
Jakubowska, Anna, Cybulski, Cezary, Szymanska, Anna et al. (2008) BARD1 and breast cancer in Poland. Breast cancer research and treatment 107(1): 119-22	- Study design does not match that specified in this review protocol
Janezic, S A, Ziogas, A, Krumroy, L M et al. (1999) Germline BRCA1 alterations in a population-based series of ovarian cancer cases. Human molecular genetics 8(5): 889-97	- Population in study does not match that specified in this review protocol
John EM, Miron A, Gong G et al. (2007) Prevalence of pathogenic BRCA1 mutation carriers in 5 US racial/ethnic groups. JAMA 298(24): 2869-2876	- Population in study does not match that specified in this review protocol
Kronn D, Oddoux C, Phillips J et al. (1995) Prevalence of Canavan disease heterozygotes in the New York metropolitan Ashkenazi Jewish population. American journal of human genetics 57(5): 1250-1252	- Study design does not match that specified in this review protocol
Kurian, Allison W (2010) BRCA1 and BRCA2 mutations across race and ethnicity: distribution and clinical implications. Current opinion in obstetrics & gynecology 22(1): 72-8	Narrative review
Laitman, Y., Nielsen, S.M., Hatchell, K.E. et al. (2022) Re-evaluating cancer risks associated with the CHEK2 p.Ser428Phe Ashkenazi Jewish founder pathogenic variant. Familial Cancer 21(3): 305-308	- Study design does not match that specified in this review protocol
Lang, Guan-Tian, Shi, Jin-Xiu, Hu, Xin et al. (2017) The spectrum of BRCA mutations and characteristics of BRCA-associated breast cancers in China: Screening of 2,991 patients and 1,043 controls by next-generation sequencing. International journal of cancer 141(1): 129-142	- Study design does not match that specified in this review protocol
Lawniczak, M., Jakubowska, A., Biaek, A. et al. (2015) Possible association of the BRCA2 gene C5972T variant with gastric cancer: A study on Polish population. Polskie Archiwum Medycyny Wewnetrznej 125(12): 39-45	- Study design does not match that specified in this review protocol
Li, Ang, Xie, Rong, Zhi, Qihuan et al. (2018) BRCA germline mutations in an unselected nationwide cohort of Chinese patients with ovarian cancer and healthy controls. Gynecologic oncology 151(1): 145-152	- Study design does not match that specified in this review protocol
Lieberman, S., Chen-Shtoyerman, R., Levi, Z. et al. (2022) Common founder BRCA2 pathogenic variants and breast cancer characteristics in Ethiopian Jews. Breast Cancer Research and Treatment 193(1): 217-224	- Study design does not match that specified in this review protocol
Lieberman, Sari, Lahad, Amnon, Tomer, Ariela et al. (2017) Population screening for BRCA1/BRCA2 mutations: lessons from qualitative analysis of the	- Study design does not match that specified in this review protocol

Study	Reason for exclusion
screening experience. Genetics in medicine: official journal of the American College of Medical Genetics 19(6): 628-634	
Liede, Alexander, Malik, Imtiaz A, Aziz, Zeba et al. (2002) Contribution of BRCA1 and BRCA2 mutations to breast and ovarian cancer in Pakistan. American journal of human genetics 71(3): 595-606	- Study design does not match that specified in this review protocol
Liede, Alexander and Narod, Steven A (2002) Hereditary breast and ovarian cancer in Asia: genetic epidemiology of BRCA1 and BRCA2. Human mutation 20(6): 413-24	- Population in study does not match that specified in this review protocol
Liu, Yin, Liao, Ji, Xu, Ye et al. (2011) A recurrent CHEK2 p.H371Y mutation is associated with breast cancer risk in Chinese women. Human mutation 32(9): 1000-3	- Study design does not match that specified in this review protocol
Lu, K H, Cramer, D W, Muto, M G et al. (1999) A population-based study of BRCA1 and BRCA2 mutations in Jewish women with epithelial ovarian cancer. Obstetrics and gynecology 93(1): 34-7	- Study design does not match that specified in this review protocol
Makriyianni I, Hamel N, Ward S et al. (2005) BRCA1:185delAG found in the San Luis Valley probably originated in a Jewish founder. Journal of medical genetics 42(5): e27	- Data not reported in an extractable format or a format that can be analysed
Malone, K.E., Daling, J.R., Doody, D.R. et al. (2006) Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in White and Black American women ages 35 to 64 years. Cancer Research 66(16): 8297-8308	- Study design does not match that specified in this review protocol
Manchanda R, Loggenberg K, Sanderson S et al. (2015) Population testing for cancer predisposing BRCA1/BRCA2 mutations in the Ashkenazi-Jewish community: a randomized controlled trial. Journal of the National Cancer Institute 107(1): 379	- A newer study by the same author included
Manchanda, R. and Gaba, F. (2018) Population based testing for primary prevention: A systematic review. Cancers 10(11): 424	- Systematic review used as source of primary studies
Mehta, A., Diwan, H., Gupta, G. et al. (2022) Founder BRCA1 mutations in Nepalese population. Journal of Pathology and Translational Medicine 56(4): 212-216	- Population in study does not match that specified in this review protocol
Metcalfe, Kelly A, Mian, Nida, Enmore, Melissa et al. (2012) Long-term follow-up of Jewish women with a BRCA1 and BRCA2 mutation who underwent population genetic screening. Breast cancer research and treatment 133(2): 735-40	- Data not reported in an extractable format or a format that can be analysed
Miron, A., Schildkraut, J.M., Rimer, B.K. et al. (2000) Testing for hereditary breast and ovarian cancer in the southeastern United States. Annals of Surgery 231(5): 624-634	- Population in study does not match that specified in this review protocol
Modan, B., Hartge, P., Hirsh-Yechezkel, G. et al. (2001) Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. New England Journal of Medicine 345(4): 235-240	- Study design does not match that specified in this review protocol

Study	Reason for exclusion
Modan, B, Gak, E, Sade-Bruchim, R B et al. (1996) High frequency of BRCA1 185delAG mutation in ovarian cancer in Israel. National Israel Study of Ovarian Cancer. JAMA 276(22): 1823-5	- Study design does not match that specified in this review protocol
Mohamad, S., Isa, N.M., Muhammad, R. et al. (2015) Low prevalence of CHEK2 gene mutations in multiethnic cohorts of breast cancer patients in Malaysia. PLoS ONE 10(1): e0117104	- Study design does not match that specified in this review protocol
Mullineaux, L.G., Castellano, T.M., Shaw, J. et al. (2003) Identification of germline 185delAG BRCA1 mutations in non-Jewish Americans of Spanish ancestry from the San Luis Valley, Colorado. Cancer 98(3): 597-602	- Study design does not match that specified in this review protocol
Muto, M.G., Cramer, D.W., Tangir, J. et al. (1996) Frequency of the BRCA1 185delAG mutation among Jewish women with ovarian cancer and matched population controls. Cancer Research 56(6): 1250-1252	- Study design does not match that specified in this review protocol
Newman, B., Mu, H., Butler, L.M. et al. (1998) Frequency of breast cancer attributable to BRCA1 in a population-based series of American women. JAMA 279(12): 915-921	- Study design does not match that specified in this review protocol
Oddoux, C, Struewing, J P, Clayton, C M et al. (1996) The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. Nature genetics 14(2): 188-90	- Study design does not match that specified in this review protocol
Offit, K., Gilad, S., Paglin, S. et al. (2002) Rare variants of ATM and risk for Hodgkin's disease and radiation-associated breast cancers. Clinical Cancer Research 8(12): 3813-3819	- Study design does not match that specified in this review protocol
Offit, K., Pierce, H., Kirchhoff, T. et al. (2003) Frequency of CHEK2*1100delC in New York breast cancer cases and controls. BMC Medical Genetics 4: 1	- Study design does not match that specified in this review protocol
Ossa, C.A. and Torres, D. (2016) Founder and recurrent mutations in BRCA1 and BRCA2 genes in Latin American Countries: State of the art and literature review. Oncologist 21(7): 832-839	- Narrative review
Palmer, Julie R, Polley, Eric C, Hu, Chunling et al. (2020) Contribution of Germline Predisposition Gene Mutations to Breast Cancer Risk in African American Women. Journal of the National Cancer Institute 112(12): 1213-1221	- Study design does not match that specified in this review protocol
Park, K.-S., Lee, W.-C., Seong, M.-W. et al. (2021) A population-based analysis of brca1/2 genes and associated breast and ovarian cancer risk in Korean patients: A multicenter cohort study. Cancers 13(9): 2192	- Population in study does not match that specified in this review protocol
Phuah, Sze Yee, Lee, Sheau Yee, Kang, Peter et al. (2013) Prevalence of PALB2 mutations in breast cancer patients in multi-ethnic Asian population in Malaysia and Singapore. PloS one 8(8): e73638	- Study design does not match that specified in this review protocol
Pölsler L, Fiegl H, Wimmer K et al. (2016) High prevalence of BRCA1 stop mutation c.4183C>T in the Tyrolean population: implications for genetic testing.	- Population in study does not match that specified in this review protocol

Study	Reason for exclusion
European journal of human genetics: EJHG 24(2): 258-262	
Ramus, S.J., Song, H., Dicks, E. et al. (2015) Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. Journal of the National Cancer Institute 107(11)	- Study design does not match that specified in this review protocol
Raskin, L., Schwenter, F., Freytsis, M. et al. (2011) Characterization of two Ashkenazi Jewish founder mutations in MSH6 gene causing Lynch syndrome. Clinical Genetics 79(6): 512-522	- Study design does not match that specified in this review protocol
Rebbeck, Timothy R, Friebel, Tara M, Friedman, Eitan et al. (2018) Mutational spectrum in a worldwide study of 29,700 families with BRCA1 or BRCA2 mutations. Human mutation 39(5): 593-620	- Population in study does not match that specified in this review protocol
Rivera-Herrera, A.-L., Cifuentes-C, L., Gil-Vera, J.A. et al. (2018) Absence of the CHEK2 c.1100delc mutation in familial breast and ovarian cancer in Colombia: A case-control study. F1000Research 7: 1032	- Study design does not match that specified in this review protocol
Rogoza-Janiszewska, E., Malinska, K., Gorski, B. et al. (2021) Prevalence of germline TP53 variants among early-onset breast cancer patients from Polish population. Breast Cancer 28(1): 226-235	- Study design does not match that specified in this review protocol
Rosenthal, Eric, Moyes, Kelsey, Arnell, Christopher et al. (2015) Incidence of BRCA1 and BRCA2 non-founder mutations in patients of Ashkenazi Jewish ancestry. Breast cancer research and treatment 149(1): 223-7	- Population in study does not match that specified in this review protocol
Salo-Mullen, E.E., Maio, A., Mukherjee, S. et al. (2021) Prevalence and characterization of biallelic and monoallelic nthl1 and msh3 variant carriers from a pan-cancer patient population. JCO Precision Oncology 5: 455-465	- Study design does not match that specified in this review protocol
Satagopan, J.M., Boyd, J., Kauff, N.D. et al. (2002) Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clinical Cancer Research 8(12): 3776-3781	- Study design does not match that specified in this review protocol
Schayek, Hagit, De Marco, Luiz, Starinsky-Elbaz, Sigal et al. (2016) The rate of recurrent BRCA1, BRCA2, and TP53 mutations in the general population, and unselected ovarian cancer cases, in Belo Horizonte, Brazil. Cancer genetics 209(12): 50-2	- Data not reported in an extractable format or a format that can be analysed
Sharma, Babita, Preet Kaur, Raman, Raut, Sonali et al. (2018) BRCA1 mutation spectrum, functions, and therapeutic strategies: The story so far. Current problems in cancer 42(2): 189-207	- Narrative review
Sobczak, K, Kozlowski, P, Napierala, M et al. (1997) Novel BRCA1 mutations and more frequent intron-20 alteration found among 236 women from Western Poland. Oncogene 15(15): 1773-9	- Study design does not match that specified in this review protocol
Song, H, Dicks, E, Ramus, SJ et al. (2015) Contribution of Germline Mutations in the RAD51B, RAD51C, and	- Study design does not match that specified in this review

Study	Reason for exclusion
RAD51D Genes to Ovarian Cancer in the Population. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 33(26): 2901-7	protocol
Struewing JP, Hartge P, Wacholder S et al. (1997) The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. The New England journal of medicine 336(20): 1401-1408	- Data not reported in an extractable format or a format that can be analysed
Suchy, Janina, Cybulski, Cezary, Gorski, Bohdan et al. (2010) BRCA1 mutations and colorectal cancer in Poland. Familial cancer 9(4): 541-4	- Study design does not match that specified in this review protocol
Szwiec, Marek, Tomiczek-Szwiec, Joanna, Kluzniak, Wojciech et al. (2021) Genetic predisposition to male breast cancer in Poland. BMC cancer 21(1): 975	- Study design does not match that specified in this review protocol
Vogel, K.J., Atchley, D.P., Erlichman, J. et al. (2007) BRCA1 and BRCA2 genetic testing in Hispanic patients: Mutation prevalence and evaluation of the BRCAPRO risk assessment model. Journal of Clinical Oncology 25(29): 4635-4641	- Study design does not match that specified in this review protocol
Wang, W W, Spurdle, A B, Kolachana, P et al. (2001) A single nucleotide polymorphism in the 5' untranslated region of RAD51 and risk of cancer among BRCA1/2 mutation carriers. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 10(9): 955-60	- Study design does not match that specified in this review protocol
Warner, E, Foulkes, W, Goodwin, P et al. (1999) Prevalence and penetrance of BRCA1 and BRCA2 gene mutations in unselected Ashkenazi Jewish women with breast cancer. Journal of the National Cancer Institute 91(14): 1241-7	- Study design does not match that specified in this review protocol
Wenham, Robert M, Schildkraut, Joellen M, McLean, Kia et al. (2003) Polymorphisms in BRCA1 and BRCA2 and risk of epithelial ovarian cancer. Clinical cancer research: an official journal of the American Association for Cancer Research 9(12): 4396-403	- Study design does not match that specified in this review protocol
Whittemore, A.S., Gong, G., John, E.M. et al. (2004) Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiology Biomarkers and Prevention 13(12): 2078-2083	- Population in study does not match that specified in this review protocol
Yang, S Y, Aisimutula, D, Li, H F et al. (2015) Mutational analysis of BRCA1/2 gene and pathologic characteristics from Kazakh population with sporadic breast cancer in north western China. Genetics and molecular research: GMR 14(4): 13151-61	- Study design does not match that specified in this review protocol
Zayas-Villanueva, OA, Campos-Acevedo, LD, Lugo-Trampe, JJ et al. (2019) Analysis of the pathogenic variants of BRCA1 and BRCA2 using next-generation sequencing in women with familial breast cancer: a case-control study. BMC cancer 19(1): 722	- Study design does not match that specified in this review protocol

Study	Reason for exclusion
Zhi, Wenxian, Xue, Binshuang, Wang, Lifeng et al. (2011) The MLH1 2101C>A (Q701K) variant increases the risk of gastric cancer in Chinese males. BMC gastroenterology 11: 133	- Study design does not match that specified in this review protocol

Excluded economic studies

See Supplement 2 for the list of excluded studies across all reviews.

Appendix K Research recommendations

Research recommendations for review question: Which populations with a high prevalence of pathogenic variants for familial ovarian cancer would meet the risk threshold for genetic testing?

No research recommendations were made for this review question.