National Institute for Health and Care Excellence

Draft for consultation

Ovarian cancer: identifying and managing familial and genetic risk

[C] Configuration of services

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.1.1 to 1.1.8 and research recommendations in the NICE guideline

September 2023

Draft for consultation

These evidence reviews were developed by NICE

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ISBN:

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Review question

What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

Introduction

Women with a familial risk of ovarian cancer are asked to manage a complex set of health needs. They need to understand their lifetime risk of ovarian cancer and decide upon interventions that can impact on their fertility, self-image, and menopause status. In addition, surgical interventions are not without their own set of risks. Services need to be established that can holistically support women with a familial risk of ovarian cancer through this process. However, the exact nature and composition and configuration is not fully known.

Herein we discuss the evidence base for these recommendations and outline how these services should be commissioned. Where there is a lack of evidence, we will also outline key research priorities.

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	Women with familial ovarian cancer or at likely increased risk of familial ovarian cancer

Intervention	Any service delivery models (approaches, configurations of resources and services) for referral, risk assessment and risk management for women at increased risk of ovarian cancer. For example:
	
	Delivery arrangements:
	• How, when and where assessments are done, for example:
	  ○ referral from primary care
	  ○ direct to consumer tests
	• Who does assessments:
	  ○ mainstreaming of genetic testing for affected women (within oncology clinic vs. traditional genetic counselling model within clinical genetics)
	  ○ pathology reporting (for example, double reporting)
	• Coordination of care and management of care processes, for example:
	  ○ one stop clinics (multiple specialties within the same clinic, for example, *BRCA* carrier clinics)
	  ○ multidisciplinary teams/working
	  ○ access to psychological, menopause and fertility services
	  ○ combined surgical procedures (for example, risk reducing mastectomy, risk reducing salpingo-oophorectomy)
	  ○ coordination of assessments amongst different providers

Comparison	Interventions compared with: • Each other • Combinations of interventions

Outcomes	**Critical**
	• Overall survival
	• Quality of life
	• Patient satisfaction
	Important
	• Access to services:
	  ○ Local availability (for example, time/distance travelled to access services)
	  ○ Waiting times for services
	  ○ Time to diagnosis or identification of a familial risk
	  ○ Time to treatment (risk reducing)
	  ○ Access to clinical trials

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).

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

Effectiveness/ Service delivery evidence

Included studies

Eleven observational studies were included for this review. They compared a variety of service delivery models mainly against a standard service delivery, and mainly in women with ovarian cancer.

Three studies compared a mainstreaming cancer genetic testing/counselling/service with no mainstreaming cancer genetic service in women with ovarian cancer (Ip 2020, Yoon 2022) and in women with breast cancer (Scott 2020).

One study compared a streamlined pre-test genetic education and genetic testing service with a standard service delivery in women with ovarian cancer (Powell 2020).

Two studies compared a gynaecologic oncologist-initiated genetic testing service with a standard genetic testing service (Piedimonte 2020, Rumford 2020).

Three studies compared a model with the addition of an embedded genetic counsellor in the medical and/or gynaecologic oncology clinic with a standard service delivery (Rana 2021, Senter 2017, Warias 2021).

One study compared a reflex *BRCA1/2* tumour testing with a no reflex *BRCA1/2* tumour testing in women with ovarian cancer (McCuaig 2020).

One study compared a multidisciplinary one-stop follow-up clinic with a no multidisciplinary one-stop follow-up clinic in *BRCA1/2* carriers (Pichert 2010).

The included studies are summarised in Table 2.

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 K.

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	Intervention*	Comparison*	Outcomes
Ip 2022 Retrospective cohort Australia	N=289 women with ovarian cancer Age, median (range), years: 60 (34-93)	Mainstream germline genetic testing program	Cancer genetic service	• Time to diagnosis or identification of a familial risk ○ Time from blood collection to report
McCuaig 2020 Retrospective cohort Canada	N=212 (analysed n=175) women with newly diagnosed high-grade serous ovarian cancer (including cases of primary peritoneal or fallopian tube cancers) Age, median (range), years: 63.8 (38.1-90)	Reflex *BRCA1/2* tumour testing	No Reflex *BRCA1/2* tumour testing	• Time to diagnosis or identification of a familial risk ○ Time to referral for genetic counselling
Pichert 2010 Retrospective cohort UK	N=172 *BRCA1/2* carriers who choose to attend the MDOSC Age, years: out of 164 women <20=1%, 21-30=9%, 31-40=27%, 41-50=29%, 51-60=20%, 61-70=13%, >71=1%	Multidisciplinary one-stop follow-up clinic (MDOSC)	No MDOSC	• Access to clinical trials ○ Recruitment to trials
Piedimonte 2020 Retrospective case series Canada	N=152 patients diagnosed with high-grade serous ovarian, tubal, or peritoneal cancer Age: not reported	Gynaecologic oncologist-initiated genetic testing model	Traditional genetics referral-based program	• Time to diagnosis or identification of a familial risk ○ Time from diagnosis to genetic testing ○ Delay between testing and result
Powell 2020	N=141 women with newly diagnosed	Streamlined pre-test genetic education and	Current standard process of	• Time to diagnosis or identification of a familial risk

Study	Population	Intervention*	Comparison*	Outcomes
Prospective cohort USA	epithelial ovarian, fallopian tube and peritoneal cancer Age, median, years: streamlining group 63.5; standard testing group 65	genetic panel testing	referral for genetic counselling and testing	○ Time from diagnosis to genetic test result ○ Time from diagnosis to notification of test result • Patient satisfaction
Rana 2021 Prospective cohort USA	N=254 women ovarian, fallopian, or primary peritoneal carcinomas Age, n, years: in the intervention group 50-59=36 (30.3%), 60-69=37 (31.1%); in comparison group 50-59=39 (28.9%), 60-69=44 (32.6%)	Addition of an embedded genetic counsellor in the medical and gynaecologic oncology clinic	Standard medical and gynaecologic oncology clinic	• Time to diagnosis or identification of a familial risk ○ Time to genetic counselling • Time to treatment (risk reducing) ○ Proportion of patients seen for ovarian cancer treatment who received genetic testing within 3 months of their initial visit
Rumford 2020 Retrospective cohort UK	N=255 ovarian cancer patients, previously untested for germline *BRCA* mutations, but n=199 samples used for the outcome of the mean time between blood sample acquisition and return of *BRCA* result to the treating oncologist (not clear how many in each group) Age, mean (range), years: 62.2 (31-91)	Oncologist-led *BRCA* testing mainstreaming service	Standard *BRCA* testing service before the implementation of mainstreaming service	• Time to diagnosis or identification of a familial risk ○ Time between blood sample acquisition and return of *BRCA* result
Scott 2020 Retrospective cohort UK	Women who were having a diagnostic genetic test because they had a positive breast cancer diagnosis. Specialist, nurse-led mainstreaming cancer genetics service n=290, Pre-MCG service	Specialist, nurse-led mainstreaming cancer genetics service (MCG)	Pre-MCG service	• Time to diagnosis or identification of a familial risk ○ Time from testing until genetic test result

Study	Population	Intervention*	Comparison*	Outcomes
	= not reported, data based on average service data Age, mean (range), years (reported for those in the intervention group only): 2016 = 47.44 (23-70), 2017 = 49.81 (29-70), 2018 = 48.9 (24-80)			
Senter 2017 Retrospective cohort USA	N=737 patients with newly diagnosed ovarian cancer Age: not reported	Genetics embedded model (GEM; incorporates a cancer genetic counsellor on-site in the gynaecologic oncology clinic)	No genetics-embedded model of service (cancer genetics services provided as an off-site consultation)	• Time to diagnosis or identification of a familial risk ○ Time from referral to scheduling in genetics ○ Time from referral to completion of genetics consultation
Warias 2021 Retrospective cohort Canada	N=386 women with a new pathologic diagnosis of epithelial ovarian cancer Age (n), years: in the intervention group: =>60 = 29 (34%), <60=56 (66%); in the comparison group: =>60 = 214 (71%), <60=87 (29%)	Collaborative care model involving the integration of genetic counsellors into tumour board round	No collaborative care model	• Time to diagnosis or identification of a familial risk ○ Time from diagnosis to referral ○ Time from referral to first appointment
Yoon 2022 Prospective cohort Malaysia	N=790 but analysed n=512 women with newly diagnosed with non-mucinous ovarian, fallopian tube or primary peritoneal cancer Age, mean (SD), years: 52.4 (10.8)	Mainstreaming genetic counselling	Standard genetics referral pathway	• Quality of life ○ Psychosocial impact • Patient satisfaction ○ Satisfaction with genetic counselling

1 *GEM: genetics embedded model; MCG: mainstreaming cancer genetics; MDOSC: multidisciplinary one-stop*
2 *follow-up clinic; SD: standard deviation*
3 **for details see Appendix D: Evidence tables*

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

Studies reported a variety of different configuration services for referral, risk assessment and management, therefore it is difficult to draw an overall conclusion. Effect estimates could not be calculated for all studies as not all of them reported relevant data, therefore some of the results reported here are based on the significance or non-significance of the findings reported in the studies.

Women with ovarian cancer

Mainstream germline genetic testing program versus cancer genetic service

Low quality evidence comparing mainstream genetic testing to the cancer genetic service was inconclusive in terms of time from blood collection to report/return to the treating oncologist. Although it was not reported whether there was a statistical difference between the mainstream genetic testing and the standard genetic service, it was reported that the average time from blood collection to report was 7 days longer with the mainstream genetic testing program than with the cancer genetic service.

Mainstreaming genetic counselling versus standard genetics referral pathway

Very low to moderate quality evidence indicated no important difference in terms of either psychosocial aspects within the cancer genetic counselling setting (a proxy for quality of life) or with the genetic counselling satisfaction among women participating in the mainstreaming genetic counselling as compared to the standard cancer referral pathway.

Streamlined pre-test genetic education and genetic panel testing versus standard counselling and testing

One study did not report whether time from diagnosis to genetic test result or to blood draw was significantly different between a streamlined pre-test genetic education and genetic panel testing service delivery model (where testing is provided by the managing gynaecologic oncologists) and the standard counselling and testing. However, it reported that the time from diagnosis to genetic test result (median 12 days shorter) and also to blood draw (median 7 days shorter) was shorter with the streamlined pre-test genetic education and genetic testing panel testing service as compared to the current counselling and testing.

Very low to low quality evidence showed no important difference in terms of patient satisfaction associated with the genetic testing, including, for example, uncertainty, positive experience, satisfaction with time for discussion and adequacy of information provided and others when compared the streamlined pre-test genetic education and genetic panel testing with the current counselling and testing. In terms of distress associated with genetic testing, there was no evidence of an important difference between the two services (low quality evidence).

Gynaecologic oncologist-initiated genetic testing model versus traditional genetics referral

Very low quality evidence showed a shorter time from diagnosis to genetic testing (median 114 days shorter) and a shorter delay between the testing and the result (median 20.5 days shorter) with the gynaecologic oncologist-initiated genetic testing model as compared to the traditional care model It is not clear whether there was a significant difference between the two models in terms of the above outcomes as it was not reported in the study.

In terms of time between blood sample acquisition and return of the result to the treating oncologist, it is not clear whether there was any significant difference between the two

models as it was not reported. However, it was reported that the turnaround time was shorter (mean 127.6 days shorter) with the gynaecologic oncologist-initiated genetic testing model.

Embedded genetic counsellor in the medical and gynaecologic oncology clinic versus standard clinic

Low quality evidence showed a shorter time from initial consultation to genetic counselling or from referral to scheduling in genetics, and to completion of genetics consultation with an embedded genetic counsellor in the medical/gynaecologic oncology clinic or with a cancer genetic counsellor on-site in the gynaecologic oncology clinic as compared to standard care models. In terms of the proportion of patients seen for ovarian cancer treatment who received genetic testing within 3 months of their initial visit (a proxy for the time to treatment outcome), moderate quality evidence showed an important benefit of the service with an embedded genetic counsellor as compared to the standard service.

Genetics embedded model versus no genetic embedded model

One study reported a shorter time from referral to scheduling in genetics (mean 3.13 months) and to completion of genetics consultation (mean 0.85 months) with the genetics embedded model as compared to no genetics embedded model (moderate quality evidence).

Collaborative care model versus no collaborative care model

In terms of time from diagnosis to referral and also to first appointment, one study reported a shorter time with the collaborative care model involving the integration of genetic counsellors into tumour board round as compared to no collaborative care model (low quality evidence).

Reflex BRCA1/2 testing versus no reflex testing

Very low quality evidence from 1 study assessing the reflex *BRCA1/2* tumour testing (where genetic testing of tumour tissue is initiated by a pathologist as part of surgical pathology review) reported a shorter time to referral for genetic counselling (median 26 days shorter) with the reflex tumour testing model as compared to the no reflex tumour testing model.

Women with breast cancer

Nurse-led mainstreaming cancer genetics (MCG) service verses pre-MCG service

Very low quality evidence from 1 study assessing a specialist, nurse-led mainstreaming cancer genetics service in women with a positive breast cancer diagnosis having a genetic test was inconclusive as it did not report whether there was a statistical difference between the specialist, nurse-led mainstreaming cancer genetic service and the usual service in terms of time from genetic testing to the test result.

***BRCA1/2* carriers**

Multidisciplinary one-stop follow-up clinic verses no one-stop clinic

In terms of the recruitment to trials, moderate quality evidence showed an important benefit of the multidisciplinary clinic as compared to no multidisciplinary clinic.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

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

No economic studies were identified which were applicable to this review question.

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

No economic studies were identified which were applicable to this review question.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Overall survival and quality of life were prioritised as critical outcomes by the committee because they indicate the impact of services on the long-term health and wellbeing of those at increased risk of ovarian cancer. Patient satisfaction was also a critical outcome as a way of comparing the relative acceptability of different service configurations.

Access to services was chosen an important outcome to capture the efficiency and convenience of different service models. Examples of access were local availability, waiting times for services, time to diagnosis or identification of a familial risk, time to treatment (risk reducing), and access to clinical trials.

The quality of the evidence

The quality of the evidence from the included studies was assessed with GRADE and was rated as mainly very low or low mainly due to serious risk of bias of individual studies and in some cases also due to imprecision of the estimate. Serious risk of bias was typically due to incomplete adjustment for confounders, so baseline differences between people seen in different service configurations could bias the results.

There was no evidence identified for overall survival and local availability. This meant that the committee used their experience and expertise to estimate the longer term impact of different service configurations.

Benefits and harms

The committee noted that the variety of configurations of services reported in the evidence made it difficult to identify a single ideal service configuration, but they noted that certain features such as embedded specialisms within the team, mainstreaming of genetic counselling and teams that collaborated were associated with important benefits, that is better outcomes such as shorter waiting times for referral, and subsequently to genetic

counselling and testing. The relatively small number of studies and uncertainties about the reported effects and the way the studies were conducted meant the recommendations were largely based on their knowledge and experience.

The committee explained that there are well-established referral mechanisms and pathways to clinical genetics. However, there is variation in the referral criteria, the minimum dataset accepted prior to referral, and also among clinicians in primary and secondary care regarding whether and how to make a referral. Therefore, the committee aimed to provide guidance that should help reduce this variation in practice.

They agreed, based on their experience, that referral pathways from primary or secondary care for people at risk of having a pathogenic variant associated with ovarian cancer could be facilitated by clear referral criteria, an online referral form for referral, family history questionnaire filled out by the affected person, and standardised patient information leaflets (for example, a web page or paper form). For example, currently some genetic specialist services do not accept patients without a detailed family history, including a family history questionnaire streamlines the referral process. The committee also agreed that laying out specific referral criteria would help the referring clinician and standardise the process.

The committee discussed, based on their experience, that some people such as those with physical, cognitive or sensory disabilities, some diverse ethnic groups as well as men, trans people and non-binary people may be under referred to genetic services and they agreed to recommend equality and inclusiveness training, and information provision for healthcare professionals in primary and secondary care to address this.

The committee agreed that primary care healthcare professionals have a limited capacity to seek out potential index cases, however, in cases where family history is known, they can make a referral to genetic services. Based on their experience, the committee listed the main responsibilities of primary care healthcare professionals such as providing information and support and referral to genetic services and/or other specialist services.

The committee agreed to list the main responsibilities of the genetic services including providing information and support, pathogenic variant risk assessment, genetic counselling and testing, cascade testing of relatives, discussion of potential management options and referral to the familial ovarian cancer multidisciplinary team, so people know what to expect when referred.

Based on the evidence which showed some important benefits of genetic testing and counselling where the gynaecology oncology team takes responsibility, the committee agreed that genetic counselling and testing of women with a histopathological diagnosis of epithelial ovarian cancer should be carried out by their gynaecology oncology multidisciplinary team. They agreed that in general the evidence indicated that counselling provided within the gynaecology oncology multidisciplinary team would be more efficient and faster for women with ovarian cancer to access than referral to genetics services.

The committee discussed the management of people who carry a pathogenic variant and those who are above a risk threshold. The committee acknowledged the significant variation in practice in the way risk is managed for this population. To standardise practice and provide coordinated lifelong care for people at risk of familial ovarian cancer the committee agreed to list the responsibilities of the MDT and also a familial ovarian cancer multidisciplinary team approach consisting of members from clinical genetics, gynaecology and gynaecological oncology would be the most appropriate. This was also partly based on the evidence about the multidisciplinary management of people who are carriers of pathogenic variants, which showed better recruitment to clinical trials with a multidisciplinary one-stop follow-up clinic.

The committee agreed patients would require access to a range of different services during their lifetime which they do not currently always have direct access to, for example, fertility or

menopause services. They therefore decided to recommend that there are agreed referral pathways to other specialist services through the familial ovarian cancer multidisciplinary team.

Cost effectiveness and resource use

There was no existing economic evidence identified for this review.

The committee noted the existence of variation in the referral criteria, the minimum dataset accepted prior to referral, and also practices among clinicians in primary and secondary care regarding whether and how to make a referral. Therefore, the recommendation in this area should help reduce such variation in practice. There was some discussion about family history questionnaires and it was noted that patients are generally responsible for their completion. It was agreed that an online referral form to specialist services could be completed within minutes, for example by GPs.

This recommendation may also result in an increased number of people accessing genetic services, potentially creating additional pressure on existing services. However, the committee explained that the costs associated with genetic testing and counselling are low compared with the potential benefits. Identifying people with pathogenic variants could significantly reduce their risk of cancer and associated costs.

There are various training programmes on equality and inclusiveness issues available for NHS staff. The recommendation for this will not require services to set up new training, create new information resources nor is it expected to require additional resources to implement.

The committee discussed primary care and genetic services' responsibilities for people at risk of familial ovarian cancer. This recommendation represents current practice and will not require additional resources to implement. Similarly, the committee explained that people diagnosed with epithelial ovarian cancer would be under the care of gynaecology oncology multidisciplinary team who would be initiating genetic counselling and testing which is current practice across services. Reducing these variations will also help to ensure that people have equal access to genetic testing.

The committee discussed familial ovarian cancer multidisciplinary teams' composition, roles and responsibilities. These teams may not exist in every cancer centre and recommendations on this may represent a change in practice for some services. Most cancer services are expected to have access to psychological services, menopause services etc. This recommendation is about ensuring that multidisciplinary teams have links to existing specialist services and do not require establishment of new services.

The committee noted that support services should have the capacity to meet the referrals from ovarian cancer services. However, the committee highlighted that some services have staff shortages, which may impact the implementation of this recommendation. It was also acknowledged that due to the more streamlined organisation of services for people with familial ovarian cancer, more people might access support services earlier, potentially creating additional pressure on the services. Nevertheless, the committee agreed that under resourcing of services should not prevent them making recommendations on access to such services.

There was further discussion about how these multidisciplinary teams are set up. They explained that while access to specialists is essential and the overall care is coordinated by them, physical co-location of these specialists in a single clinic is not required. The committee was of a view that setting up familial ovarian cancer multidisciplinary teams, in cases where they are currently lacking, is unlikely to require significant resources. They noted that any additional costs associated with setting up these teams would be outweighed by the benefits they offer, including coordinated and timely access to appropriate care, such

as risk-reducing surgery. These teams can effectively reduce individuals' cancer risk and associated care costs.

Other factors the committee took into account

The committee discussed that there were some configuration of service models which were not included in this review because they were not comparative. They mentioned the mainstream genetic testing pathway in which testing was undertaken by the trained cancer team with cascade testing to relatives performed by the genetics team (George et al. 2016). This testing pathway showed that the mainstream *BRCA* testing required fewer appointments, fewer referrals to genetics teams and was quicker overall. However, this study did not impact the recommendations.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1 to 1.1.8 in the NICE guideline.

References – included studies

Effectiveness

Ip 2022

Ip, E., Young, A.L., Scheinberg, T. et al. (2022) Evaluation of a mainstream genetic testing program for women with ovarian or breast cancer. Asia-Pacific Journal of Clinical Oncology First published: 30 January 2022

McCuaig 2020

McCuaig, Jeanna M, Care, Melanie, Ferguson, Sarah E et al. (2020) Year 1: Experiences of a tertiary cancer centre following implementation of reflex BRCA1 and BRCA2 tumor testing for all high-grade serous ovarian cancers in a universal healthcare system. Gynecologic oncology 158(3): 747-753

Pichert 2010

Pichert, G, Jacobs, C, Jacobs, I et al. (2010) Novel one-stop multidisciplinary follow-up clinic significantly improves cancer risk management in BRCA1/2 carriers. Familial cancer 9(3): 313-9

Piedimonte 2020

Piedimonte, Sabrina, Power, Joanne, Foulkes, William D et al. (2020) BRCA testing in women with high-grade serous ovarian cancer: gynecologic oncologist-initiated testing compared with genetics referral. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 30(11): 1757-1761

Powell 2020

Powell, C Bethan, Laurent, Cecile, Ciaravino, Giuseppe et al. (2020) Streamlining genetic testing for women with ovarian cancer in a Northern California health care system. Gynecologic oncology 159(1): 221-228

Rana 2021

Rana, Huma Q, Kipnis, Lindsay, Hehir, Kristin et al. (2021) Embedding a genetic counselor into oncology clinics improves testing rates and timeliness for women with ovarian cancer. Gynecologic oncology 160(2): 457-463

Rumford 2020

Rumford, M., Lythgoe, M., McNeish, I. et al. (2020) Oncologist-led BRCA 'mainstreaming' in the ovarian cancer clinic: A study of 255 patients and its impact on their management. Scientific Reports 10(1): 3390

Scott 2020

Scott N, O'Sullivan J, Asgeirsson K et al. (2020) Changing practice: moving to a specialist nurse-led service for BRCA gene testing. British journal of nursing (Mark Allen Publishing) 29(10): S6-S13

Senter 2017

Senter, Leigha, O'Malley, David M, Backes, Floor J et al. (2017) Genetic consultation embedded in a gynecologic oncology clinic improves compliance with guideline-based care. Gynecologic oncology 147(1): 110-114

Warias 2021

Warias, Ashley, Ferguson, Meghan, Chamberlain, Erin et al. (2021) Universal access to genetic counseling for women with epithelial ovarian cancer in Nova Scotia: Evaluating a new collaborative care model. Journal of genetic counseling 30(5): 1491-1499

Yoon 2022

Yoon, Sook-Yee, Wong, Siu Wan, Lim, Joanna et al. (2022) Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. Journal of medical genetics 59(3): 220-229

References - other

George, A, Riddell, D, Seal, S et al. (2016) Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Scientific Reports 13(6): 29506

Appendices

Appendix A Review protocol

Review protocol for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022360499
1.	Review title	Effective configuration of services for referral, risk assessment and risk management
2.	Review question	What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?
3.	Objective	To establish effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Emcare • Epistemonikos • MEDLINE & MEDLINE In-Process • HMIC (Kings Fund)

		Searches will be restricted by: • Systematic review/meta-analysis study design filter • RCT/non-randomised controlled trials study design filter • Date: 1995 • English language studies • Human studies Other searches: • Reference searching • Citation searching • Inclusion lists of systematic reviews • Websites 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: women with familial ovarian cancer or at likely increased risk of familial ovarian cancer Exclusion: none

7.	Intervention	Any service delivery models (approaches, configurations of resources and services) for referral, risk assessment and risk management for women at increased risk of ovarian cancer. For example:
		
		Delivery arrangements:
		• How, when and where assessments are done, for example:
		  ○ referral from primary care
		  ○ direct to consumer tests
		• Who does assessments:
		  ○ mainstreaming of genetic testing for affected women (within oncology clinic vs. traditional genetic counselling model within clinical genetics)

		○ pathology reporting (for example, double reporting) • Coordination of care and management of care processes, for example: ○ one stop clinics (multiple specialties within the same clinic, for example, *BRCA* carrier clinics) ○ multidisciplinary teams/working ○ access to psychological, menopause and fertility services ○ combined surgical procedures (for example, risk reducing mastectomy, risk reducing salpingo-oophorectomy) ○ coordination of assessments amongst different providers
8.	Comparator/Reference standard/Confounding factors	Interventions compared with: • Each other • Combinations of interventions
9.	Types of study to be included	• Randomised controlled trials • Non-randomised comparative studies (including before & after designs) • Systematic reviews/meta-analyses • Service evaluations and audits
10.	Other exclusion criteria	**Inclusion**: • Full text papers **Exclusion**: • Conference abstracts • Articles published before 1995 • 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	Possible overlap with CG164 (Familial Breast Cancer) which covers referral to genetic services.
12.	Primary outcomes (critical outcomes)	• Overall survival • Quality of life • Patient satisfaction

13.	Secondary outcomes (important outcomes)	• Access to services:
		  ○ Local availability (for example, time/distance travelled to access services)
		  ○ Waiting times for services
		  ○ Time to diagnosis or identification of a familial risk
		  ○ Time to treatment (risk reducing)
		  ○ Access to clinical trials

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; 90% agreement is required. 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. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. 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 Appendix H of Developing NICE guidelines: the manual • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • The non-randomised study design appropriate checklist. For example, Cochrane ROBINS-I tool for non-randomised controlled trials and cohort studies; the EPOC RoB tool for controlled before and after 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. Data Synthesis Where possible, pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events. Mean differences or standardised mean differences will be calculated for continuous outcomes. If sufficient RCTs are available forming a network of relevant interventions, network meta-analysis will be done using MetaInsight V3 (Owen, RK, Bradbury, N, Xin, Y, Cooper, N, Sutton, A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Syn Meth. 2019; 10: 569-581) Heterogeneity Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. In the case of serious or very serious unexplained heterogeneity (remaining after pre-specified subgroup and stratified analyses) meta-analysis will be done using a random effects model. Minimal important differences (MIDs) Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes • For risk ratios: 0.8 and 1.25. • For continuous outcomes: o MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. o For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. 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:
		• Patients (such as those with pathological variants) managed in multidisciplinary high risk clinics versus elsewhere
		
		Evidence will be subgrouped by the following only in the event that there is serious heterogeneity in outcomes:
		• Subgroups listed in the equality impact assessment form:
		  ○ 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 (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	September 2022		
22.	Anticipated completion date	2023		
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 Guideline Alliance **5b Named contact e-mail** focl@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		

25.	Review team members	Guideline development team NGA Technical Team: • Senior systematic reviewer • Systematic reviewer
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from 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?RecordID=360499
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	Ovarian cancer, service, delivery, referral assessment
33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing

		☐ Completed but not published ☒ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None
36.	Details of final publication	www.nice.org.uk

GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; SMD: standard mean difference

Appendix B Literature search strategies

Literature search strategies for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

Database: MEDLINE ALL

Date of last search: 24/01/2023

#	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*)).tw,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*)).tw,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*)).tw,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
14	HNPCC.tw,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,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)).tw,kf.
18	gardner* syndrome*.tw,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).tw,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*)).tw,kf.
21	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,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*)).tw,kf.
23	risk factors/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
25	((carrier* or gene*) adj3 mutat*).tw,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*))).tw,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
30	exp Fanconi Anemia Complementation Group Proteins/
31	(Fanconi An?emia adj3 protein*).tw,kf.
32	(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.
33	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
34	Rad51 Recombinase/
35	Ataxia Telangiectasia Mutated Proteins/

#	Searches
36	((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.
37	Checkpoint Kinase 2/
38	(((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.
39	Carcinoma, Small Cell/ge [Genetics]
40	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
41	(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.
42	exp Sertoli-Leydig Cell Tumor/
43	(((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.
44	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
45	Epithelial Cell Adhesion Molecule/
46	Epithelial cell adhesion molecule*.tw,kf.
47	(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.
48	or/9-47
49	8 and 48
50	exp Health Services/
51	exp Patient Care Management/ or intersectoral collaboration/ or "Interinstitutional Relations"/
52	Ambulatory Care/ or Ambulatory Care Facilities/
53	models, organizational/
54	((care or service* or delivery* or navigat*) adj3 (model* or configur* or approach* or system* or pathway* or program* or coordinat* or co ordinat* or manag* or support* or level* or standard* or comprehensive)).ti,ab,kf.
55	(hospital* or facilit* or centre* or center* or service* or clinic* or unit* or site* or department*).ti,ab,kf.
56	(speciali* or expert* or expertise).ti,ab,kf.
57	Practice Guidelines as Topic/
58	exp Interprofessional Relations/
59	(multicomponent* or multi* component or integrat* or multi* disciplin* or multidisciplin* or multiprofession* or multi profession* or interprofession* or inter profession* or interdisciplin* or inter disciplin* or transprofession* or trans profession* or intersect* or inter sect* or overarch* or side by side or collaborat* or MDC or MDT or IDT or MDOSC).ti,ab,kf.
60	mainstream*.ti,ab,kf.
61	((onestop or one stop) adj3 shop*).ti,ab,kf.
62	Cancer Care Facilities/
63	"Direct-To-Consumer Screening and Testing"/
64	((direct* or initiat*) adj2 (consumer* or access*) adj2 (test* or screen*)).ti,ab,kf.
65	Mobile Applications/
66	exp Internet/
67	exp Cell Phone/
68	exp Computers, Handheld/
69	Medical Informatics Applications/
70	Therapy, Computer-Assisted/
71	(app or apps).ti,ab,kf.
72	(online or web or internet or digital*).ti.
73	((online or web or internet or digital*) adj3 (based or application* or intervention* or program* or therap*)).ab.
74	(phone* or telephone* or smartphone* or cellphone* or smartwatch*).ti.
75	((phone* or telephone* or smartphone* or cellphone* or smartwatch*) adj3 (based or application* or intervention* or program* or therap*)).ab.
76	(mobile health or mhealth or m health or ehealth or e health or emental or e mental).ti.
77	((mobile health or mhealth or m health or ehealth or e health or emental or e mental) adj3 (based or application* or intervention* or program* or therap*)).ab.
78	(mobile* adj3 (based or application* or intervention* or device* or technolog*)).ti,ab.
79	or/50-78
80	Menopause, Premature/ or Menopause/ or Perimenopause/ or Postmenopause/ or Premenopause/

#	Searches
81	(menopaus* or perimenopaus* or peri menopaus* or postmenopaus* or post menopaus* or POF).ti,ab,kf.
82	Climacteric/
83	climacteri*.ti,ab,kf.
84	Fertility/
85	(fertility or fecundity or onocofertility).ti,ab,kf.
86	General Surgery/
87	exp Mastectomy/
88	Salpingo-oophorectomy/
89	(surger* or surgical or mastectom* or mammaplast* or mammoplast* or mammectom* or oophorectom* or salpingooophorectom*).ti,ab,kf.
90	(risk reduc* adj surger*).ti,ab,kf.
91	exp Counseling/ or Genetic Counseling/
92	psychology/ or psychology, social/ or Psycho-Oncology/
93	(counsel* or psycho* or therap*).ti,ab,kf.
94	or/80-93
95	49 and 79 and 94
96	Risk Management/ or Risk Assessment/ or Risk Factors/ or Risk Reduction Behavior/ or Needs Assessment/
97	((risk* or likelihood or need*) adj3 (assess* or manag* or analys?s or classif* or categor* or factor* or predict* or estimat* or identif* or reduc*)).ti,ab,kf.
98	"Referral and Consultation"/
99	(refer* or recommend* or advi?e* or assess* or reassess* or re assess* or consult* or evaluat* or re evaluat* or followup* or follow up*).ti,ab,kf.
100	second opinion*.ti,ab,kf.
101	or/96-100
102	49 and 79 and 101
103	95 or 102
104	letter/
105	editorial/
106	news/
107	exp historical article/
108	Anecdotes as Topic/
109	comment/
110	case reports/
111	(letter or comment*).ti.
112	or/104-111
113	randomized controlled trial/ or random*.ti,ab.
114	112 not 113
115	animals/ not humans/
116	exp Animals, Laboratory/
117	exp Animal Experimentation/
118	exp Models, Animal/
119	exp Rodentia/
120	(rat or rats or mouse or mice or rodent*).ti.
121	or/114-120
122	103 not 121
123	limit 122 to English language
124	randomized controlled trial.pt.
125	controlled clinical trial.pt.
126	pragmatic clinical trial.pt.
127	randomi#ed.ab.
128	placebo.ab.
129	drug therapy.fs.
130	randomly.ab.
131	trial.ab.

#	Searches
132	groups.ab.
133	or/124-132
134	Clinical Trials as topic.sh.
135	trial.ti.
136	or/124-128,130,134-135
137	Meta-Analysis/
138	Meta-Analysis as Topic/
139	(meta analy* or metanaly* or metaanaly*).ti,ab.
140	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
141	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
142	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
143	(search* adj4 literature).ab.
144	(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.
145	cochrane.jw.
146	or/137-145
147	123 and (136 or 146)
148	Observational Studies as Topic/
149	Observational Study/
150	Epidemiologic Studies/
151	exp Case-Control Studies/
152	exp Cohort Studies/
153	Cross-Sectional Studies/
154	Controlled Before-After Studies/
155	Historically Controlled Study/
156	Interrupted Time Series Analysis/
157	Comparative Study.pt.
158	case control$.tw.
159	case series.tw.
160	(cohort adj (study or studies)).tw.
161	cohort analy$.tw.
162	(follow up adj (study or studies)).tw.
163	(observational adj (study or studies)).tw.
164	longitudinal.tw.
165	prospective.tw.
166	retrospective.tw.
167	cross sectional.tw.
168	or/148-167
169	123 and 168
170	169 not 147
171	limit 147 to ed=19950101-20230120
172	limit 147 to dt=19950101-20230120
173	171 or 172
174	limit 170 to ed=19950101-20230120
175	limit 170 to dt=19950101-20230120
176	174 or 175

1 **Database: Embase**

2 **Date of last search: 24/01/2023**

#	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.

#	Searches
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	Fanconi anemia protein/
30	(Fanconi An?emia adj3 protein*).tw,kf.
31	(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.
32	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
33	Rad51 protein/
34	ATM protein/
35	((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.
36	checkpoint kinase 2/
37	(((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.
38	small cell carcinoma/
39	genetics/
40	38 and 39
41	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
42	(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.
43	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
44	(((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.
45	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
46	epithelial cell adhesion molecule/

#	Searches
47	Epithelial cell adhesion molecule*.tw,kf.
48	(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.
49	or/8-37,40-48
50	7 and 49
51	exp health service/
52	exp patient care/ or intersectoral collaboration/
53	ambulatory care/ or outpatient department/
54	nonbiological model/
55	((care or service* or delivery* or navigat*) adj3 (model* or configur* or approach* or system* or pathway* or program* or coordinat* or co ordinat* or manag* or support* or level* or standard* or comprehensive)).ti,ab,kf.
56	(hospital* or facilit* or centre* or center* or service* or clinic* or unit* or site* or department*).ti,ab,kf.
57	(speciali* or expert* or expertise).ti,ab,kf.
58	practice guideline/
59	public relations/
60	(multicomponent* or multi* component or integrat* or multi* disciplin* or multidisciplin* or multiprofession* or multi profession* or interprofession* or inter profession* or interdisciplin* or inter disciplin* or transprofession* or trans profession* or intersect* or inter sect* or overarch* or side by side or collaborat* or MDC or MDT or IDT or MDOSC).ti,ab,kf.
61	mainstream*.ti,ab,kf.
62	((onestop or one stop) adj3 shop*).ti,ab,kf.
63	cancer center/
64	screening test/
65	((direct* or initiat*) adj2 (consumer* or access*) adj2 (test* or screen*)).ti,ab,kf.
66	exp mobile application/
67	internet/
68	exp mobile phone/
69	computer assisted therapy/
70	personal digital assistant/
71	text messaging/
72	(app or apps).ti,ab.
73	(online or web or internet or digital*).ti.
74	((online or web or internet or digital*) adj3 (based or application* or intervention* or program* or therap*)).ab.
75	(phone* or telephone* or smartphone* or cellphone* or smartwatch*).ti.
76	((phone* or telephone* or smartphone* or cellphone* or smartwatch*) adj3 (based or application* or intervention* or program* or therap*)).ab.
77	(mobile health or mhealth or m health or ehealth or e health or emental or e mental).ti.
78	((mobile health or mhealth or m health or ehealth or e health or emental or e mental) adj3 (based or application* or intervention* or program* or therap*)).ab.
79	(mobile* adj3 (based or application* or intervention* or device* or technolog*)).ti,ab.
80	or/51-79
81	exp "menopause and climacterium"/
82	(menopaus* or perimenopaus* or peri menopaus* or postmenopaus* or post menopaus* or POF).ti,ab,kf.
83	climacteri*.ti,ab,kf.
84	exp fertility/
85	(fertility or fecundity or onocofertility).ti,ab,kf.
86	general surgery/
87	exp mastectomy/
88	exp salpingooophorectomy/
89	(surger* or surgical or mastectom* or mammaplast* or mammoplast* or mammectom* or oophorectom* or salpingooophorectom*).ti,ab,kf.
90	(risk reduc* adj surger*).ti,ab,kf.
91	exp counseling/
92	psychology/ or social psychology/ or psycho-oncology/
93	(counsel* or psycho* or therap*).ti,ab,kf.

#	Searches
94	or/81-93
95	50 and 80 and 94
96	risk management/ or risk assessment/ or risk factor/ or risk reduction/ or needs assessment/
97	((risk* or likelihood or need*) adj3 (assess* or manag* or analys?s or classif* or categor* or factor* or predict* or estimat* or identif* or reduc*)).ti,ab,kf.
98	patient referral/ or "evaluation and follow up"/ or follow up/
99	(refer* or recommend* or advi?e* or assess* or reassess* or re assess* or consult* or evaluat* or re evaluat* or followup* or follow up*).ti,ab,kf.
100	second opinion*.ti,ab,kf.
101	or/96-100
102	50 and 80 and 101
103	95 or 102
104	letter.pt. or letter/
105	note.pt.
106	editorial.pt.
107	case report/ or case study/
108	(letter or comment*).ti.
109	or/104-108
110	randomized controlled trial/ or random*.ti,ab.
111	109 not 110
112	animal/ not human/
113	nonhuman/
114	exp Animal Experiment/
115	exp Experimental Animal/
116	animal model/
117	exp Rodent/
118	(rat or rats or mouse or mice or rodent*).ti.
119	or/111-118
120	103 not 119
121	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
122	120 not 121
123	limit 122 to English language
124	random*.ti,ab.
125	factorial*.ti,ab.
126	(crossover* or cross over*).ti,ab.
127	((doubl* or singl*) adj blind*).ti,ab.
128	(assign* or allocat* or volunteer* or placebo*).ti,ab.
129	crossover procedure/
130	single blind procedure/
131	randomized controlled trial/
132	double blind procedure/
133	or/124-132
134	systematic review/
135	meta-analysis/
136	(meta analy* or metanaly* or metaanaly*).ti,ab.
137	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
138	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
139	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
140	(search* adj4 literature).ab.
141	(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.
142	((pool* or combined) adj2 (data or trials or studies or results)).ab.
143	cochrane.jw.
144	or/134-143

#	Searches
145	123 and (133 or 144)
146	Clinical study/
147	Case control study/
148	Family study/
149	Longitudinal study/
150	Retrospective study/
151	comparative study/
152	Prospective study/
153	Randomized controlled trials/
154	152 not 153
155	Cohort analysis/
156	cohort analy$.tw.
157	(Cohort adj (study or studies)).tw.
158	(Case control$ adj (study or studies)).tw.
159	(follow up adj (study or studies)).tw.
160	(observational adj (study or studies)).tw.
161	(epidemiologic$ adj (study or studies)).tw.
162	(cross sectional adj (study or studies)).tw.
163	case series.tw.
164	prospective.tw.
165	retrospective.tw.
166	or/146-151,154-165
167	123 and 166
168	167 not 145
169	limit 145 to dc=19950101-20230120
170	limit 168 to dc=19950101-20230120

1 Database: Ovid Emcare

2 Date of last search: 24/01/2023

#	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.

#	Searches
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	Fanconi anemia protein/
30	(Fanconi An?emia adj3 protein*).tw,kf.
31	(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.
32	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
33	Rad51 protein/
34	ATM protein/
35	((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.
36	checkpoint kinase 2/
37	(((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.
38	small cell carcinoma/
39	genetics/
40	38 and 39
41	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
42	(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.
43	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
44	(((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.
45	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
46	epithelial cell adhesion molecule/
47	Epithelial cell adhesion molecule*.tw,kf.
48	(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.
49	or/8-37,40-48
50	7 and 49
51	exp health service/
52	exp patient care/ or intersectoral collaboration/
53	ambulatory care/ or outpatient department/
54	nonbiological model/
55	((care or service* or delivery* or navigat*) adj3 (model* or configur* or approach* or system* or pathway* or program* or coordinat* or co ordinat* or manag* or support* or level* or standard* or comprehensive)).ti,ab,kf.
56	(hospital* or facilit* or centre* or center* or service* or clinic* or unit* or site* or department*).ti,ab,kf.
57	(speciali* or expert* or expertise).ti,ab,kf.
58	practice guideline/
59	public relations/
60	(multicomponent* or multi* component or integrat* or multi* disciplin* or multidisciplin* or multiprofession* or multi profession* or interprofession* or inter profession* or interdisciplin* or inter disciplin* or transprofession* or trans profession* or intersect* or inter sect* or overarch* or side by side or collaborat* or MDC or MDT or IDT or MDOSC).ti,ab,kf.
61	mainstream*.ti,ab,kf.

#	Searches
62	((onestop or one stop) adj3 shop*).ti,ab,kf.
63	cancer center/
64	screening test/
65	((direct* or initiat*) adj2 (consumer* or access*) adj2 (test* or screen*)).ti,ab,kf.
66	exp mobile application/
67	internet/
68	exp mobile phone/
69	computer assisted therapy/
70	personal digital assistant/
71	text messaging/
72	(app or apps).ti,ab.
73	(online or web or internet or digital*).ti.
74	((online or web or internet or digital*) adj3 (based or application* or intervention* or program* or therap*)).ab.
75	(phone* or telephone* or smartphone* or cellphone* or smartwatch*).ti.
76	((phone* or telephone* or smartphone* or cellphone* or smartwatch*) adj3 (based or application* or intervention* or program* or therap*)).ab.
77	(mobile health or mhealth or m health or ehealth or e health or emental or e mental).ti.
78	((mobile health or mhealth or m health or ehealth or e health or emental or e mental) adj3 (based or application* or intervention* or program* or therap*)).ab.
79	(mobile* adj3 (based or application* or intervention* or device* or technolog*)).ti,ab.
80	or/51-79
81	exp "menopause and climacterium"/
82	(menopaus* or perimenopaus* or peri menopaus* or postmenopaus* or post menopaus* or POF).ti,ab,kf.
83	climacteri*.ti,ab,kf.
84	exp fertility/
85	(fertility or fecundity or onocofertility).ti,ab,kf.
86	general surgery/
87	exp mastectomy/
88	exp salpingooophorectomy/
89	(surger* or surgical or mastectom* or mammaplast* or mammoplast* or mammectom* or oophorectom* or salpingooophorectom*).ti,ab,kf.
90	(risk reduc* adj surger*).ti,ab,kf.
91	exp counseling/
92	psychology/ or social psychology/ or psycho-oncology/
93	(counsel* or psycho* or therap*).ti,ab,kf.
94	or/81-93
95	50 and 80 and 94
96	risk management/ or risk assessment/ or risk factor/ or risk reduction/ or needs assessment/
97	((risk* or likelihood or need*) adj3 (assess* or manag* or analys?s or classif* or categor* or factor* or predict* or estimat* or identif* or reduc*)).ti,ab,kf.
98	patient referral/ or "evaluation and follow up"/ or follow up/
99	(refer* or recommend* or advi?e* or assess* or reassess* or re assess* or consult* or evaluat* or re evaluat* or followup* or follow up*).ti,ab,kf.
100	second opinion*.ti,ab,kf.
101	or/96-100
102	50 and 80 and 101
103	95 or 102
104	letter.pt. or letter/
105	note.pt.
106	editorial.pt.
107	case report/ or case study/
108	(letter or comment*).ti.
109	or/104-108
110	randomized controlled trial/ or random*.ti,ab.
111	109 not 110

#	Searches
112	animal/ not human/
113	nonhuman/
114	exp Animal Experiment/
115	exp Experimental Animal/
116	animal model/
117	exp Rodent/
118	(rat or rats or mouse or mice or rodent*).ti.
119	or/111-118
120	103 not 119
121	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
122	120 not 121
123	limit 122 to English language
124	random*.ti,ab.
125	factorial*.ti,ab.
126	(crossover* or cross over*).ti,ab.
127	((doubl* or singl*) adj blind*).ti,ab.
128	(assign* or allocat* or volunteer* or placebo*).ti,ab.
129	crossover procedure/
130	single blind procedure/
131	randomized controlled trial/
132	double blind procedure/
133	or/124-132
134	systematic review/
135	meta-analysis/
136	(meta analy* or metanaly* or metaanaly*).ti,ab.
137	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
138	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
139	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
140	(search* adj4 literature).ab.
141	(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.
142	((pool* or combined) adj2 (data or trials or studies or results)).ab.
143	cochrane.jw.
144	or/134-143
145	123 and (133 or 144)
146	Clinical study/
147	Case control study/
148	Family study/
149	Longitudinal study/
150	Retrospective study/
151	comparative study/
152	Prospective study/
153	Randomized controlled trials/
154	152 not 153
155	Cohort analysis/
156	cohort analy$.tw.
157	(Cohort adj (study or studies)).tw.
158	(Case control$ adj (study or studies)).tw.
159	(follow up adj (study or studies)).tw.
160	(observational adj (study or studies)).tw.
161	(epidemiologic$ adj (study or studies)).tw.
162	(cross sectional adj (study or studies)).tw.
163	case series.tw.
164	prospective.tw.

#	Searches
165	retrospective.tw.
166	or/146-151,154-165
167	123 and 166

1

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

4 **Date of last search: 26/01/2023**

#	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	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#31	(("Fanconi Anemia" or "fanconi anaemia") NEAR/3 protein*):ti,ab,kw
#32	(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
#33	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#34	MeSH descriptor: [Rad51 Recombinase] this term only

#	Searches
#35	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#36	(("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
#37	MeSH descriptor: [Checkpoint Kinase 2] this term only
#38	(((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
#39	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]
#40	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#41	(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
#42	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#43	(((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
#44	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H48 LIKE"):ti,ab,kw
#45	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#46	Epithelial cell adhesion NEXT molecule*:ti,ab,kw
#47	(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
#48	{OR #9-#47}
#49	#8 AND #48
#50	MeSH descriptor: [Health Services] explode all trees
#51	MeSH descriptor: [Patient Care Management] explode all trees
#52	MeSH descriptor: [Intersectoral Collaboration] this term only
#53	MeSH descriptor: [Interinstitutional Relations] this term only
#54	MeSH descriptor: [Ambulatory Care] this term only
#55	MeSH descriptor: [Ambulatory Care Facilities] this term only
#56	MeSH descriptor: [Models, Organizational] this term only
#57	((care or service* or delivery* or navigat*) NEAR/3 (model* or configur* or approach* or system* or pathway* or program* or coordinat* or co ordinat* or manag* or support* or level* or standard* or comprehensive)):ti,ab,kw
#58	(hospital* or facilit* or centre* or center* or service* or clinic* or unit* or site* or department*):ti,ab,kw
#59	(speciali* or expert* or expertise):ti,ab,kw
#60	MeSH descriptor: [Practice Guidelines as Topic] this term only
#61	MeSH descriptor: [Interprofessional Relations] explode all trees
#62	(multicomponent* or multi* NEXT component or integrat* or multi* NEXT disciplin* or multidisciplin* or multiprofession* or multi NEXT profession* or interprofession* or inter NEXT profession* or interdisciplin* or inter NEXT disciplin* or transprofession* or trans NEXT profession* or intersect* or inter NEXT sect* or overarch* or "side by side" or collaborat* or MDC or MDT or IDT or MDOSC):ti,ab,kw
#63	mainstream*:ti,ab,kw
#64	((onestop or "one stop") NEAR/3 shop*):ti,ab,kw
#65	MeSH descriptor: [Cancer Care Facilities] this term only
#66	MeSH descriptor: [Direct-To-Consumer Screening and Testing] this term only
#67	((direct* or initiat*) NEAR/2 (consumer* or access*) NEAR/2 (test* or screen*)):ti,ab,kw
#68	MeSH descriptor: [Mobile Applications] this term only
#69	MeSH descriptor: [Internet] explode all trees
#70	MeSH descriptor: [Cell Phone] 1 tree(s) exploded
#71	MeSH descriptor: [Computers, Handheld] explode all trees
#72	MeSH descriptor: [Medical Informatics Applications] this term only
#73	MeSH descriptor: [Therapy, Computer-Assisted] this term only
#74	(app or apps):ti,ab,kw
#75	(online or web or internet or digital*):ti
#76	((online or web or internet or digital*) NEAR/3 (based or application* or intervention* or program* or therap*)):ab
#77	(phone* or telephone* or smartphone* or cellphone* or smartwatch*):ti
#78	((phone* or telephone* or smartphone* or cellphone* or smartwatch*) NEAR/3 (based or application* or intervention* or program* or therap*)):ab
#79	(mobile health or mhealth or "m health" or ehealth or "e health" or emental or "e mental"):ti
#80	((mobile health or mhealth or "m healt" or ehealth or "e health" or emental or "e mental") NEAR/3 (based or application*

#	Searches
	or intervention* or program* or therap*)):ab
#81	(mobile* NEAR/3 (based or application* or intervention* or device* or technolog*)):ti,ab
#82	{OR #50-#81}
#83	MeSH descriptor: [Menopause, Premature] this term only
#84	MeSH descriptor: [Menopause] this term only
#85	MeSH descriptor: [Perimenopause] this term only
#86	MeSH descriptor: [Postmenopause] this term only
#87	MeSH descriptor: [Premenopause] this term only
#88	(menopaus* or perimenopaus* or peri NEXT menopaus* or postmenopaus* or post NEXT menopaus* or POF):ti,ab,kw
#89	MeSH descriptor: [Climacteric] this term only
#90	climacteri*:ti,ab,kw
#91	MeSH descriptor: [Fertility] this term only
#92	(fertility or fecundity or onocofertility):ti,ab,kw
#93	MeSH descriptor: [General Surgery] this term only
#94	MeSH descriptor: [Mastectomy] explode all trees
#95	MeSH descriptor: [Salpingo-oophorectomy] this term only
#96	(surger* or surgical or mastectom* or mammaplast* or mammoplast* or mammectom* or oophorectom* or salpingooophorectom*):ti,ab,kw
#97	(risk NEXT reduc* NEAR surger*):ti,ab,kw
#98	MeSH descriptor: [Counseling] explode all trees
#99	MeSH descriptor: [Genetic Counseling] this term only
#100	MeSH descriptor: [Psychology] this term only
#101	MeSH descriptor: [Psychology, Social] this term only
#102	MeSH descriptor: [Psycho-Oncology] this term only
#103	(counsel* or psycho* or therap*):ti,ab,kw
#104	{or #83-#103}
#105	#49 and #82 and #104
#106	MeSH descriptor: [Risk Management] this term only
#107	MeSH descriptor: [Risk Assessment] this term only
#108	MeSH descriptor: [Risk Factors] this term only
#109	MeSH descriptor: [Risk Reduction Behavior] this term only
#110	MeSH descriptor: [Needs Assessment] this term only
#111	((risk* or likelihood or need*) NEAR/3 (assess* or manag* or analysis or analyses or classif* or categor* or factor* or predict* or estimat* or identif* or reduc*)):ti,ab,kw
#112	MeSH descriptor: [Referral and Consultation] this term only
#113	(refer* or recommend* or advice* or advise* or assess* or reassess* or re assess* or consult* or evaluat* or re evaluat* or followup* or follow NEXT up*):ti,ab,kw
#114	second NEXT opinion*:ti,ab,kw
#115	{or #106-#114}
#116	#49 and #82 and #115
#117	#105 or #116
#118	conference:pt or (clinicaltrials or trialsearch):so
#119	#117 not #118 with Cochrane Library publication date Between Jan 1995 and Jan 2023

1 Database: Epistemonikos

2 Date of last search: 02/09/2022

#	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:((care OR service* OR delivery* OR navigat* OR followup)) OR advanced_abstract_en:((care OR service* OR delivery* OR navigat* OR followup))
3	en:((advanced_title_en:((multicomponent* OR multi* component OR integrat* OR multi* disciplin* OR multidisciplin* OR multiprofession* OR multi profession* OR interprofession* OR inter profession* OR interdisciplin* OR inter disciplin* OR transprofession* OR trans profession* OR intersect* OR inter sect* OR overarch* OR side by side OR collaborat* OR MDC OR MDT OR IDT OR MDOSC)) OR advanced_abstract_en:((multicomponent* OR multi* component OR integrat* OR multi* disciplin* OR multidisciplin* OR multiprofession* OR multi profession* OR interprofession* OR inter

#	Searches
	profession* OR interdisciplin* OR inter disciplin* OR transprofession* OR trans profession* OR intersect* OR inter sect* OR overarch* OR side by side OR collaborat* OR MDC OR MDT OR IDT OR MDOSC))
4	2 OR 3
5	1 AND 4
	[Filters: protocol=no, classification=systematic-review, cochrane=missing, min_year=1995, max_year=2022]

1 **Database: HMIC Kings Fund**

2 **Date of last search: 01/09/2022**

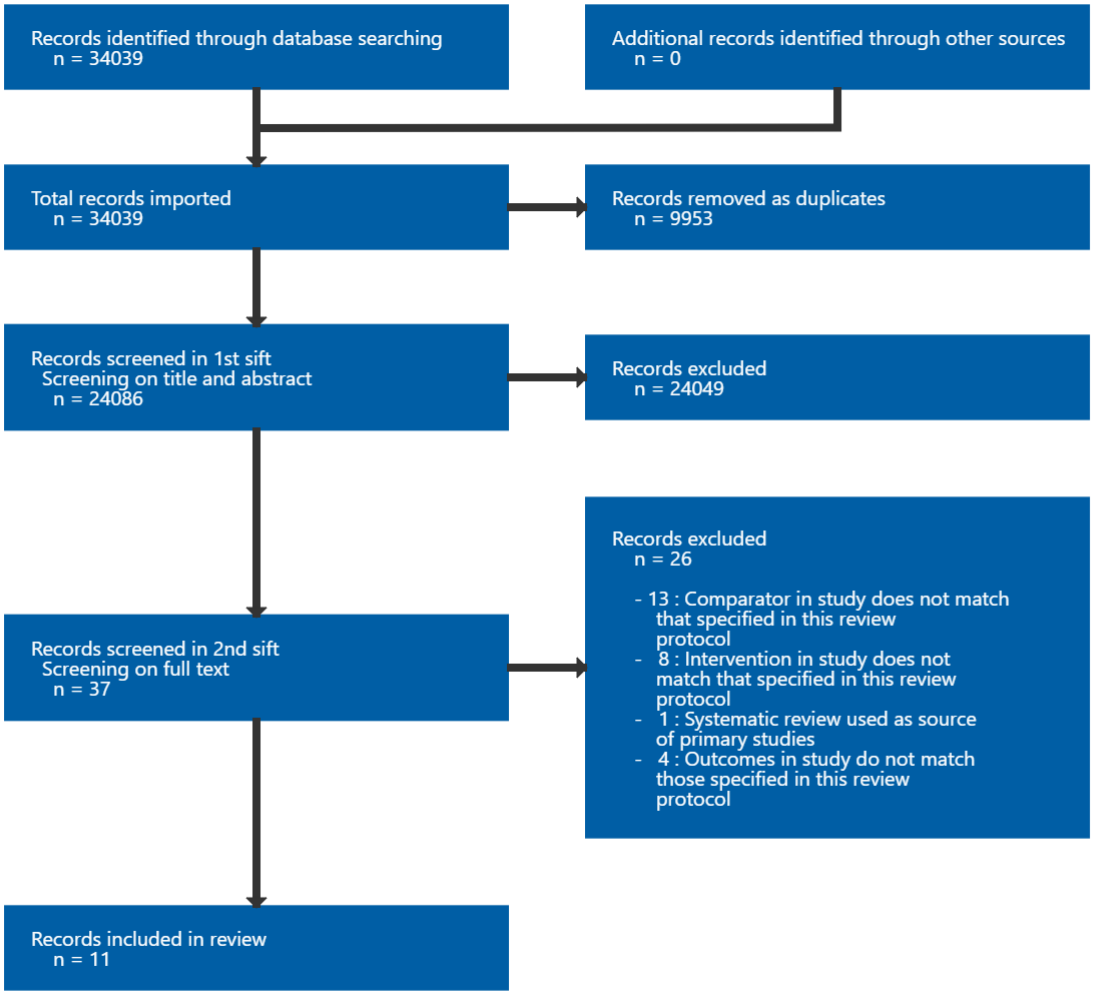
#	Searches
1	ovarian cancer* or breast cancer*
2	service*
	1 and 2
	limit to 1995-

3

Appendix C Effectiveness/Service delivery evidence study selection

Study selection for: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

Ip, 2022

Bibliographic Reference Ip, E.; Young, A.L.; Scheinberg, T.; Harrison, M.; Beale, P.; Goodwin, A.; Evaluation of a mainstream genetic testing program for women with ovarian or breast cancer; Asia-Pacific Journal of Clinical Oncology; 2022

Study details

Country/ies where study was carried out	Australia
Study type	Retrospective cohort study electronic and written medical records review
Study dates	February 2015 and August 2019
Inclusion criteria	• Women diagnosed with high grade non-mucinous epithelial ovarian, fallopian tube or primary peritoneal cancer (hereto referred to as ovarian cancer) and who consented to genetic testing via the mainstreaming program or the Cancer Genetic Service (CGS). • Women who consented to genetic testing. • Women were assessed as eligible for genetic testing if it was possible to determine from the medical record that they met the 10% threshold for detecting a *BRCA1/2* pathogenic variant according to National guidelines or, after 2017, for women who qualified for treatment-focused testing to define potential olaparib access.
Exclusion criteria	Not reported
Patient characteristics	N=289 women with ovarian cancer who consented to genetic testing; n=138 (66%) were consented by mainstreaming and n=71 (34%) by genetic testing arranged by the CGS.

	Gender: Women **Age (years, median (range)) at genetic testing:** 60 (34-93) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported **With breast cancer diagnosis, n:** 17 (8.1%)
Intervention(s)/control	• Mainstream germline genetic testing program Established in 2015 to facilitate germline genetic testing by a patient's treating medical oncologist arranged with the support of the local Cancer Genetic Service (CGS). In this program genetic testing was arranged only by medical oncologists. Individualized training was provided to medical oncologists who were interested in participating in the program. Patients were flagged as eligible by their oncologist, during MDT meetings, or by directly contacting the CGS. The medical oncologist arranged pre-test counselling and consent and disclosed the genetic test result to the patient. • Cancer Genetic Service (CGS) No details given
Duration of follow-up	Not applicable
Sources of funding	Not reported
Sample size	N=289 women with ovarian cancer; n=138 (66%) mainstreaming and n=71 (34%) genetic testing arranged by the CGS

1

Study arms

Mainstream (N = 138)

Cancer genetics (N = 69)

Outcomes

Time from blood collection to report

Outcome	Mainstream, N = 138	Cancer genetics, N = 69
Time from blood collection to report: mean (range) (days) Custom value	62.6 [11-153]	55.6 [7-153]

Time from blood collection to report: mean (range) - Polarity - Lower values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate *(no description of the cancer genetic service)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

1 **McCuaig, 2020**

Bibliographic Reference McCuaig, Jeanna M; Care, Melanie; Ferguson, Sarah E; Kim, Raymond H; Stockley, Tracy L; Metcalfe, Kelly A; Year 1: Experiences of a tertiary cancer centre following implementation of reflex BRCA1 and BRCA2 tumor testing for all high-grade serous ovarian cancers in a universal healthcare system.; Gynecologic oncology; 2020; vol. 158 (no. 3); 747-753

2

3 **Study details**

Country/ies where study was carried out	Canada
Study type	Retrospective cohort study retrospective chart review
Study dates	PRE cohort: August 1, 2017 and July 31, 2018 (before implementation of reflex *BRCA1/2* tumour testing) POST cohort: October 1, 2018 and September 30, 2019 (after implementation of reflex *BRCA1/2* tumour testing)
Inclusion criteria	Cases of high-grade serous ovarian cancer (HGSOC), including primary peritoneal and fallopian tube cancers, treated at the University Health Network (UHN)'s Princess Margaret Cancer Centre in Toronto, Canada
Exclusion criteria	• since reflex *BRCA1/2* tumour testing was implemented at UHN in August 2018, cases diagnosed in August or September 2018 were excluded to allow for initial changes in patient care algorithms

	• cases with previous germline testing for hereditary cancer
Patient characteristics	N=212 (analysed n=175) cases of newly diagnosed high-grade serous ovarian cancer (HGSOC) including cases of primary peritoneal or fallopian tube cancers **Gender:** Women (although not reported) **Age (years, median (range)) at genetic testing:** 63.8 (38.1-90) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported **With breast cancer diagnosis, n:** 6 (3.4%)
Intervention(s)/control	• Reflex *BRCA1/2* tumour testing Testing of all newly diagnosed high-grade serous ovarian cancer cases, where genetic testing of tumour tissue is initiated by a pathologist as part of surgical pathology review • No reflex *BRCA1/2* testing
Duration of follow-up	Not applicable
Sources of funding	Canadian Institutes of Health Research (CIHR) Women's Health Clinical Mentorship Grant.
Sample size	N=212 (analysed n=175) cases of newly diagnosed HGSOC including cases of primary peritoneal or fallopian tube cancers; PRE cohort n=81 (46.3%), POST cohort n=94 (53.7%)

1

Study arms

PRE implementation cohort (N = 81)

POST implementation cohort (N = 94)

Outcomes

Time to referral for genetic counselling

Outcome	PRE implementation cohort, N = 81	POST implementation cohort, N = 94
Time to referral for genetic counselling: median (95% CI) (days) Custom value	59 (27.87-90.13)	33 (29.05-36.96)

Time to referral for genetic counselling: mean (95% CI) - Polarity - Lower values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

1

2 **Pichert, 2010**

Bibliographic Reference	Pichert, G; Jacobs, C; Jacobs, I; Menon, U; Manchanda, R; Johnson, M; Hamed, H; Firth, C; Evison, M; Tutt, A; de Silva, L; Langman, C; Izatt, L; Novel one-stop multidisciplinary follow-up clinic significantly improves cancer risk management in BRCA1/2 carriers.; Familial cancer; 2010; vol. 9 (no. 3); 313-9

3

4 **Study details**

Country/ies where study was carried out	UK
Study type	Retrospective cohort study
Study dates	Between February 2006 and February 2008
Inclusion criteria	*BRCA1/2* carriers
Exclusion criteria	Not reported

Patient characteristics	N=172 individuals who chose to attend the multidisciplinary one-stop follow-up clinic (MDOSC) **Gender (n):** women 164 (95%) **Age (years, n):** women: <20=1 (1%), 21-30=15 (9%), 31-40=45 (27%), 41-50=47 (29%), 51-60=33 (20%), 61-70=22 (13%), >71=1 (1%) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported
Intervention(s)/control	• Multidisciplinary one-stop follow-up clinic (MDOSC) The MDOSC was run once a month. Breast and ovarian surveillance results and histology reports of any risk reducing procedures or cancers were obtained before each clinic to inform the discussion at the MDT preceding the MDOSC where an individually tailored counselling and management strategy was devised for each patient. Patients were allocated personal consecutive 30 min appointments with each clinician they chose to see and informed on how long to expect to attend the MDOSC depending on the number of health care professionals they decided to see. • No multidisciplinary one-stop follow-up clinic No details given
Duration of follow-up	Not applicable
Sources of funding	A 24 month “New Services and Innovations in Healthcare” grant from Guy’s and St Thomas Charity was obtained to establish an MDOSC for *BRCA1/2* carriers
Sample size	N=172

1

Study arms

Multidisciplinary one-stop follow-up clinic (N = 172)

No multidisciplinary one-stop follow-up clinic (N = NR)

NR: not reported

Outcomes

Recruitment to trials

Outcome	Multidisciplinary one-stop follow-up clinic, N = 46	No multidisciplinary one-stop follow-up clinic, N = 85
Recruitment to UKFOCCS trial No of events	n = 22; % = 47.8	5; % = 5.8

Recruitment to UKFOCCS trial - Polarity - Higher values are better

Outcome	Multidisciplinary one-stop follow-up clinic, N = 126	No multidisciplinary one-stop follow-up clinic, N = 172
Recruitment to UKFOCCS trial No of events	n = 101; % = 80.2	46; % = 26.7

Recruitment to EMBRACE trial - Polarity - Higher values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate *(no description of the No multidisciplinary one-stop follow-up clinic)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

1

2 **Piedimonte, 2020**

Bibliographic Reference	Piedimonte, Sabrina; Power, Joanne; Foulkes, William D; Weber, Evan; Palma, Laura; Schiavi, Alicia; Ambrosio, Enza; Konci, Rea; Gilbert, Lucy; Jardon, Kris; Baret, Laurence; Zeng, Xing; BRCA testing in women with high-grade serous ovarian cancer: gynecologic oncologist-initiated testing compared with genetics referral.; International journal of gynecological cancer : official journal of the International Gynecological Cancer Society; 2020; vol. 30 (no. 11); 1757-1761

3

1 **Study details**

Country/ies where study was carried out	Canada
Study type	Retrospective case series
Study dates	Traditional genetics referral-based program from April 2014 to July 2017 Gynaecologic oncologist-initiated genetic testing model, after 1 year of implementation (August 2017 to August 2018).
Inclusion criteria	All patients diagnosed with high-grade serous ovarian, tubal, or peritoneal carcinoma and treated at the McGill University Health Centre, Montreal, Quebec, between January 2014 and August 2018.
Exclusion criteria	Any histology other than high-grade serous ovarian, tubal or peritoneal carcinoma, ovarian metastasis from another primary, and genetic testing in the context of a clinical trial.
Patient characteristics	N=152; n=44 included the gynaecologic oncologist-initiated genetic testing model (consecutive patients diagnosed and treated with high-grade serous ovarian, tubal, or peritoneal carcinoma); n=108 in the genetics referral group. **Gender:** not reported **Age (years, median (range)) at genetic testing:** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported ***BRCA1/2* mutations, n:** intervention group: 8 out of 54 who underwent testing; control group: 14 out of 38 who underwent testing
Intervention(s)/control	• Gynaecologic oncologist-initiated genetic testing model

	Testing was offered to all patients with newly diagnosed high-grade serous ovarian, tubal, or peritoneal carcinoma under the gynaecologic oncologist- initiated genetic testing initiative. The timeframe for the genetics referral cohort was estimated based on a similar number of high-grade serous ovarian, tubal, or peritoneal carcinoma cases per year as compared with the gynaecologic oncologist-initiated genetic testing cohort (25–40 cases). A core team comprised of a gynaecologic oncologist, genetic counsellor, and nurse worked together to develop a pathway for gynaecologic oncologist-initiated genetic testing. An algorithm was developed to outline the pathway, which included a checklist to ensure consistency of information provided to patients at the time of consent. A patient education pamphlet explaining the rationale for genetic testing, an overview of the testing process, and potential results was developed and is provided to patients at the time of consent and testing. Result disclosure was done by the genetics team, by telephone for negative results and in person for positive results for a pathogenic or likely pathogenic variant and for variants of uncertain significance, if deemed necessary. • Traditional genetics referral-based program Patients with high-grade serous ovarian, tubal, or peritoneal carcinoma were initially referred to medical genetics at the physician's discretion and based on risk factors including age, family history, or prior history of breast or ovarian cancer.
Duration of follow-up	Not applicable
Sources of funding	None reported
Sample size	N=152; n=44 included the gynaecologic oncologist-initiated genetic testing model; n=108 in the genetics referral group.

1 **Study arms**

2 **Gynaecologic oncologist-initiated genetic testing model (N = 44)**

3 **Traditional genetics referral-based program (N = 108)**

4 **Outcomes**

5 **Time from diagnosis to genetic testing**

Outcome	Gynaecologic oncologist-initiated genetic testing model, N = 44	Traditional genetics referral-based program, N = 108
Time from diagnosis to genetic testing:	40 (8-175)	154 (4-848)

Outcome	Gynaecologic oncologist-initiated genetic testing model, N = 44	Traditional genetics referral-based program, N = 108
median (range) (days) Custom value		

1 Time from diagnosis to genetic testing: median (range) - Polarity - Lower values are better

2 **Delay between testing and result**

Outcome	Gynaecologic oncologist-initiated genetic testing model, N = 44	Traditional genetics referral-based program, N = 108
Delay between testing and result: median (range) (days) Custom value	8 (8-48)	28.5 (7-271)

3 Delay between testing and result: median (range) - Polarity - Lower values are better

4

5

6 **Critical appraisal – NGA Critical appraisal - ROBINS I**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

1

2 **Powell, 2020**

Bibliographic Reference	Powell, C Bethan; Laurent, Cecile; Ciaravino, Giuseppe; Garcia, Christine; Han, Liz; Hoodfar, Elizabeth; Karlea, Audrey; Kobelka, Christine; Lee, Jaimie; Littell, Ramey D; Roh, Janise; Vay, Agniezka; Kushi, Lawrence H; Streamlining genetic testing for women with ovarian cancer in a Northern California health care system.; Gynecologic oncology; 2020; vol. 159 (no. 1); 221-228

3

4 **Study details**

Country/ies where study was carried out	USA
Study type	Prospective cohort study pilot study

Study dates	Between May and November 2019
Inclusion criteria	Women 21 years and older were eligible when seen by a study gynaecologic oncologist for a newly diagnosed epithelial ovarian, fallopian tube and peritoneal cancer.
Exclusion criteria	Women with: • a prior history of lymphoma or leukaemia • prior history of genetic referral or genetic testing for cancer risk or had a known cancer risk germline mutation in the family
Patient characteristics	n=40 women in the streamlining group and n=101 in the standard testing group **Gender:** Women **Age (years, median):** streamlining group: 63.5; standard testing group: 65 **Ethnicity (n):** streamlining group: Asian/Pacific Islander 10 (25%); Black 7 (17.5%), Hispanic 5 (12.5%), White 18 (45%); standard testing group: Asian/Pacific Islander 14 (13.9%); Black 2 (2%), Hispanic 15 (14.9%), White 64 (63.4%), Multiracial 6 (5.9%) **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (n):** streamlining group: primary language English 34 (85%), other 6 (15%); standard testing group: primary language English 96 (95.1%), other 5 (4.9%) **Non-binary people:** not reported **With personal history of breast cancer (n):** streamlining group: 2 (5%); standard testing group: 4 (4%)
Intervention(s)/control	• Streamlined pre-test genetic education and genetic panel testing Testing is provided by the managing gynaecologic oncologists for epithelial ovarian, fallopian tube and peritoneal cancer patients. The 6 gynaecologic oncologists at the two study sites underwent a 1-hour training session with the Principal

	Investigator and a genetic counsellor. Physician and patient resources were developed including a pocket checklist of key counselling points, a family history questionnaire and a Frequently Asked Questions handout. If no mutation was found, the patient was sent a letter with the panel results unless the patient had a significant family history, in which case post-test counselling was provided. If a variant of unknown significance or a pathogenic mutation were detected, the patient was contacted by the Genetics Department and post-test counselling was provided. Patients were given the option of referral via the standard pathway to see a counsellor in the Genetic Department. • Current standard Kaiser Permanente Northern California process of referral for genetic counselling and testing Guideline based and standardized throughout the regional system. The guidelines closely match National Comprehensive Community Network guidelines for referral to genetics and include all women with ovarian cancer. Any provider can refer a patient who meets regional guidelines for counselling within the system.
Duration of follow-up	Not applicable
Sources of funding	Supported by The Permanente Medical Group (TPMG) Delivery Science Research Program
Sample size	n=40 women in the streamlining group and n=101 in the standard testing group

1 **Study arms**

2 **Streamlined genetic education and testing process (N = 40)**

3 **Standard genetic testing process (N = 101)**

4 **Outcomes**

5 **Time from diagnosis to genetic test result**

Outcome	**Streamlined genetic education and testing process, N = 40**	**Standard genetic testing process, N = 101**
Time from diagnosis to genetic test result: median (days)	31	43

Outcome	Streamlined genetic education and testing process, N = 40	Standard genetic testing process, N = 101
Custom value		

1 Time from diagnosis to genetic test result: median - Polarity - Lower values are better

2 **Time from diagnosis to blood draw**

Outcome	Streamlined genetic education and testing process, N = 40	Standard genetic testing process, N = 101
Time from diagnosis to genetic test result: median (days) Custom value	18.5	25.5

3 Time from diagnosis to genetic test result: median - Polarity - Lower values are better

4 **Patient satisfaction with genetic testing**

Outcome	Streamlined genetic education and testing process, N = 37	Standard genetic testing process, N = 40
Distress Distress subscale ranges from 1=strongly agree to 5=strongly disagree Mean (SD)	3.2 (4.6)	4.5 (6.9)
Uncertainty Uncertainty subscale ranges from 0 to 45 Mean (SD)	8.5 (8.4)	8.6 (6)
Positive experience Positive experience subscale ranges from 0 to 20, polarity direction not reported	15.4 (4.6)	14 (6)

Outcome	Streamlined genetic education and testing process, N = 37	Standard genetic testing process, N = 40
Mean (SD)		
I felt satisfied with time for discussion (strongly agree) No of events	n = 21; % = 57	n = 24; % = 60
I felt adequately informed (strongly agree) No of events	n = 20	n = 22; % = 55
I had sufficient time to think (strongly agree) No of events	n = 19; % = 51	n = 23; % = 58
I was happy with the process (strongly agree) No of events	n = 22; % = 59	n = 26; % = 65
The genetic counselling provided was adequate (strongly agree) No of events	n = 20; % = 54	n = 22; % = 55
I am pleased I had the genetic test (strongly agree) No of events	n = 25; % = 68	n = 29; % = 73

1 Distress - Polarity - Lower values are better
2 Uncertainty - Polarity - Lower values are better
3 Measured using the Multidimensional Impact of Cancer Risk Assessment Questionnaire (a 25-question assessment of genetic testing
4 concerns) and 6 additional questions adapted from the George et al 2016

5

1 **Critical appraisal – NGA Critical appraisal - ROBINS I**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Patient satisfaction survey was completed by 93% of those in the streamlined testing group and by 40% of those in the standard testing group)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

2

3 **Rana, 2021**

Bibliographic Reference	Rana, Huma Q; Kipnis, Lindsay; Hehir, Kristin; Cronin, Angel; Jaung, Tim; Stokes, Samantha M; Fekrmandi, Fatemeh; Vatnick, Donna; Matulonis, Ursula A; Garber, Judy E; Wright, Alexi A; Embedding a genetic counselor into oncology clinics improves

testing rates and timeliness for women with ovarian cancer.; Gynecologic oncology; 2021; vol. 160 (no. 2); 457-463

1

2 **Study details**

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	Between 2013 and 2015, there are 2 time points are reported: before and after the genetic counsellors were embedded in the medical and gynaecologic oncology clinic (2013 vs 2014)
Inclusion criteria	Subjects with ovarian, fallopian, or primary peritoneal carcinomas (ovarian cancer) who received all or part of their treatment at Dana-Farber Cancer Institute between January 1, 2013 and December 31, 2015.
Exclusion criteria	Those with: • prior germline genetic testing, • were seen for a single consultation, • or had incomplete clinical information
Patient characteristics	n=135 in 2013 (before the genetic counsellors were embedded in the medical and gynaecologic oncology clinic) and n=119 in 2014 (after the genetic counsellors were embedded in the medical and gynaecologic oncology clinic) women diagnosed with ovarian cancer **Gender:** Women **Age at diagnosis (years, n):** 2013 cohort: <40=8 (5.9%), 40-49=18 (13.3%), 50-59=39 (28.9%), 60-69=44 (32.6%), 70-79=24 (17.8%), >=80=2 (1.5%); 2014 cohort: <40=5 (4.2%), 40-49=17 (14.3%), 50-59=36 (30.3%), 60-69=37 (31.1%), 70-79=19 (16%), >=80=5 (4.2%) **Ethnicity (n):** 2013 cohort: Non-Hispanic white 106 (78.5%), Ashkenazi Jewish 9 (6.7%), Hispanic 1 (0.7%), Non-Hispanic black 5 (3.7%), Asian/Pacific Islander 4 (3%), other/unknown 10 (7.4%); 2014 cohort: Non-Hispanic white 91 (76.55%), Ashkenazi Jewish 12 (10.1%), Hispanic 0, Non-Hispanic black 1 (0.8%), Asian/Pacific Islander 13 (10.9%),

	other/unknown 2 (1.7%) **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported
Intervention(s)/control	• Addition of an embedded genetic counsellor in the medical and gynaecologic oncology clinic A genetic counsellor was embedded in the medical and gynaecologic oncology practice as a dedicated cancer genetics provider to explicitly facilitate testing of subjects with ovarian cancer. The approach was tiered. Initially the dedicated genetic counsellor was co-located in the medical and gynaecologic oncology clinic provider workroom. The counsellor met with each of the physicians and advanced care practitioners daily and was available to meet with patients in real time, as needed. During this phase, the counsellor trained scheduling staff members to identify all patients who were newly diagnosed with ovarian cancer. Within 4 weeks, newly diagnosed patients were routinely scheduled to meet with a counsellor during their 2nd oncology visit. In addition, the counsellor was provided with a list of all patients who were newly diagnosed with ovarian cancer and those who had been previously diagnosed to ensure that all patients had undergone counselling and testing, and that all testing was up-to date. • Standard medical and gynaecologic oncology clinic No details given
Duration of follow-up	Not applicable
Sources of funding	Not reported
Sample size	n=135 in 2013 cohort and n=119 in 2014 cohort

1

Study arms

Addition of genetic counsellors in the medical and gynaecologic oncology clinic (N = 119)

Standard medical and gynaecologic oncology clinic (N = 135)

Outcomes

Time to genetic counselling

Outcome	Addition of genetic counsellors in the medical and gynaecologic oncology clinic, N = 119	Standard medical and gynaecologic oncology clinic, N = 135
Time from initial consultation and genetic counselling: median (days) Nominal	40	107

Time from initial consultation and genetic counselling: median - Polarity - Lower values are better

Proportion of patients seen for ovarian cancer treatment who received genetic testing within 3 months of their initial visit

Outcome	Addition of genetic counsellors in the medical and gynaecologic oncology clinic, N = 119	Standard medical and gynaecologic oncology clinic, N = 135
Proportion of patients seen for ovarian cancer treatment who received genetic testing within 3 months of their initial visit No of events	n = 72; % = 60	n = 45; % = 33

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate *(no description of the standard medical and gynaecologic oncology clinic)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Rumford, 2020

Bibliographic Reference	Rumford, M.; Lythgoe, M.; McNeish, I.; Gabra, H.; Tookman, L.; Rahman, N.; George, A.; Krell, J.; Oncologist-led BRCA 'mainstreaming' in the ovarian cancer clinic: A study of 255 patients and its impact on their management; Scientific Reports; 2020; vol. 10 (no. 1); 3390

1 **Study details**

Country/ies where study was carried out	UK
Study type	Retrospective cohort study review of patient clinical records
Study dates	Between April 2016 and April 2018
Inclusion criteria	All patients with a confirmed diagnosis of non-mucinous ovarian cancer and an unknown *BRCA* status who were under the care of the gynaecological oncology team at Imperial College Healthcare NHS Trust, on or after the 1st April 2016, and underwent testing.
Exclusion criteria	Those who: • had already undergone *BRCA* testing via alterative mechanisms
Patient characteristics	N=255 ovarian cancer patients, but n=199 samples used for the outcome of the mean time between blood sample acquisition and return of *BRCA* result to the treating oncologist (not clear how many in each group). **Gender:** not reported **Age (years, mean (range)) at diagnosis:** 62.2 (31-91) **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported

Intervention(s)/control	• Oncologist-led *BRCA* testing mainstreaming service The mainstreaming service could be introduced, and the patient subsequently consented for germline *BRCA* testing, by any member of the gynaecological oncology team who had completed the Mainstreaming Cancer Genetics online training program. This could occur at any scheduled appointment during the patient's treatment or routine surveillance. The consenting process involved discussion of what the *BRCA* gene is, what a mutation and variant of unknown significance is and what the relevance of the finding of a mutation might be to the patient (in terms of treatment of their ovarian cancer and future screening and prevention for other *BRCA* -associated disease) as well as the relevance of the finding to other blood relatives. Patients were given time to decide on whether they wished to proceed with BRC *BRCA* A testing and were also provided with written information developed by the oncology and genetics teams at Hammersmith Hospital and the Royal Marsden Hospital. • Standard *BRCA* testing service before the implementation of mainstreaming service No details given
Duration of follow-up	Not applicable
Sources of funding	Not reported
Sample size	N=255 ovarian cancer patients, previously untested for germline *BRCA* mutations

Study arms

Oncologist-led *BRCA* testing mainstreaming service (N = NR)

Standard *BRCA* testing service (N = NR)

Outcomes

Time between blood sample acquisition and return of *BRCA* result

Outcome	Oncologist-led *BRCA* testing mainstreaming service, N = NR	Standard *BRCA* testing service, N = NR
Time between blood sample acquisition and return of *BRCA* result	20.6 (11-42)	148.2 (98-175)

Outcome	Oncologist-led *BRCA* testing mainstreaming service, N = NR	Standard *BRCA* testing service, N = NR
to the treating oncologist: mean (range) (days) Custom value		

Time between blood sample acquisition and return of *BRCA* result to the treating oncologist: mean (range) - Polarity - Lower values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(the number of participants in each group is not clear)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate *(no description of the standard BRCA testing service)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

1

2 **Scott, 2020**

Bibliographic Reference	Scott N; O'Sullivan J; Asgeirsson K; Macmillan D; Wilson E; Changing practice: moving to a specialist nurse-led service for BRCA gene testing.; British journal of nursing (Mark Allen Publishing); 2020; vol. 29 (no. 10)

3

4 **Study details**

Country/ies where study was carried out	UK
Study type	Retrospective cohort study not entirely clear, data collected were from the mainstreaming cancer genetics database
Study dates	Pre-MCG 2014-2015 Post-MCG 2016-2018
Inclusion criteria	Women who were having a diagnostic genetic test because they had a positive breast cancer diagnosis
Exclusion criteria	Those not diagnosed with breast cancer undergoing predictive genetic testing
Patient characteristics	Reported for those in the Specialist, nurse-led mainstreaming cancer genetics service only, n=290 **Gender:** women **Age (years (mean (range)):** 2016 = 47.44 (23-70), 2017 = 49.81 (29-70), 2018 = 48.9 (24-80)

	Ethnicity (n): not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported
Intervention(s)/control	• Specialist, nurse-led mainstreaming cancer genetics service (MCG) Allows patients diagnosed with breast cancer to access genetic testing during their breast clinic appointments rather than having attend separate clinical genetics appointments. Breast clinical specialist nurses completed learning packages with local clinical genetics specialists who trained the nurses to obtain consent, council and give results for *BRCA* gene testing to patients. A weekly clinic was set up as agreed with the MDT and the clinical genetic service. Results were given to the patient by the trained breast clinical nurses and the results were also confirmed by letter following the nurse-led appointment and the breast MDT meeting. The nurses were able to directly refer patients other services, such as clinical genetics for further discussion, investigation, breast surgeons etc. • Pre-MCG service (2014-2015) Reported that details are given in Figure 1 but the figure is not available.
Duration of follow-up	Not applicable
Sources of funding	Not reported
Sample size	Specialist, nurse-led mainstreaming cancer genetics service n=290, Pre-Specialist, nurse-led mainstreaming cancer genetics service = not reported, data based on average service data

Study arms

Specialist, nurse-led mainstreaming cancer genetics service (N = 290)

Pre-Specialist, nurse-led mainstreaming cancer genetics service (N = NR)

Outcomes

Time from testing until genetic test result

Outcome	Specialist, nurse-led mainstreaming cancer genetics service, N = 290	Pre-Specialist, nurse-led mainstreaming cancer genetics service, N = NR
Time from testing until genetic test result: mean (days) NR: not reported Custom value	35.8	122 to 183

Time from testing until genetic test result: mean - Polarity - Lower values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(no adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(the total and sociodemographic characteristics of the comparison group not clear)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from	Low

Section	Question	Answer
	intended interventions	
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Senter, 2017

Bibliographic Reference	Senter, Leigha; O'Malley, David M; Backes, Floor J; Copeland, Larry J; Fowler, Jeffery M; Salani, Ritu; Cohn, David E; Genetic consultation embedded in a gynecologic oncology clinic improves compliance with guideline-based care.; Gynecologic oncology; 2017; vol. 147 (no. 1); 110-114

Study details

Country/ies where study was carried out	USA
Study type	Retrospective cohort study review of cancer patient records
Study dates	Between November 2011 and July 2016

Inclusion criteria	Newly diagnosed epithelial ovarian cancer patients
Exclusion criteria	Not reported
Patient characteristics	N=737 patients with newly diagnosed ovarian cancer **Gender:** not reported **Age (years, median (range)) at genetic testing:** not reported **Ethnicity:** not reported **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported
Intervention(s)/control	• Genetics embedded model (GEM) (incorporates a cancer genetic counsellor on-site in the gynaecologic oncology clinic) A licensed genetic counsellor was embedded in the outpatient Gynaecologic Oncology (GO) clinic on 2 full days per week at 2 locations. At least 6 full day outpatient GO clinics occur per week between two locations. When a referral is made in the electronic medical record, GO staff schedules the genetic counselling directly and does not require return of family history collection forms. An attempt was made to coordinate the genetic consultation appointments with other GO follow-up visits or treatments (for example chemotherapy infusion visits). A referral for genetic counselling was defined as the presence of a referral to cancer genetics placed in the electronic medical record any time after a GO physician saw an ovarian cancer patient who received her diagnosis during the study period. • No genetics-embedded model of service (cancer genetics services provided as an off-site consultation) Cancer genetic counselling was available as an off-site ambulatory outpatient service in the Department of Internal Medicine. Once a referral was made in the electronic medical record, genetics clinic staff would contact the patient, send them family history collection paperwork, and schedule the patient upon receipt of the family history paperwork.

Duration of follow-up	Not applicable
Sources of funding	Not reported
Sample size	N=737: n=401 pre-GEM and n=336 port-GEM

Study arms

Post-Genetics-embedded model (N = 336)

Pre-Genetics-embedded model (N = 401)

Outcomes

Time from referral to scheduling in genetics

Outcome	Post-Genetics-embedded model, N = 336	Pre-Genetics-embedded model, N = 401
Time from referral to scheduling in genetics: mean (months) A “scheduled” appointment defined as a documented appointment in the electronic health records on the clinical genetics schedule Custom value	0.79	3.92

Time from referral to scheduling in genetics: mean - Polarity - Lower values are better

Time from referral to completion of genetics consultation

Outcome	Post-Genetics-embedded model, N = 336	Pre-Genetics-embedded model, N = 401
Time from referral to completion of genetics consultation: mean (months) “Completion” of counselling defined as a closed encounter with the genetic counsellor	1.67	2.52

Outcome	Post-Genetics-embedded model, N = 336	Pre-Genetics-embedded model, N = 401
Custom value		

1 Time from referral to completion of genetics consultation: mean - Polarity - Lower values are better

2

3 **Critical appraisal – NGA Critical appraisal - ROBINS I**

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

4

1 **Warias, 2021**

Bibliographic Reference	Warias, Ashley; Ferguson, Meghan; Chamberlain, Erin; Currie, Lauren; Snow, Nicole; Matheson, Kara; Penney, Lynette S; Kieser, Katharina; Universal access to genetic counseling for women with epithelial ovarian cancer in Nova Scotia: Evaluating a new collaborative care model.; Journal of genetic counseling; 2021; vol. 30 (no. 5); 1491-1499

2

3 **Study details**

Country/ies where study was carried out	Canada
Study type	Retrospective cohort study retrospective chart review
Study dates	From 2012 to 2017
Inclusion criteria	Women with a new pathologic diagnosis of epithelial ovarian cancer (EOC)
Exclusion criteria	Women: • who did not have a diagnosis of EOC or • if time from diagnosis of ovarian cancer to death was <4 months duration.
Patient characteristics	N=386 women with EOC **Gender:** women **Age (years) at diagnosis (n):** Pre-model: =>60=214 (71%), <60=87 (29%); Post-model: =>60=29 (34%), <60=56 (66%); **Ethnicity (n):** reported only for those n=103 who participated in a survey around their experiences: Aboriginal 1 (1%), Acadian 7 (7%), African Canadian 2 (2%), European 87 (84%), mixed ethnicity 3 (3%), other 3 (3%) **Socioeconomic and geographical factors:** not reported

	Disabilities: not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported
Intervention(s)/control	• Collaborative care model involving the integration of genetic counsellors into tumour board round (as of May 2016) A genetic counsellor was in attendance at weekly gynaecologic oncology disposition rounds. This responsibility was integrated into the role of the existing genetic counselling team. Any patients with newly diagnosed epithelial ovarian cancer (EOC) were flagged and a referral for genetic counselling immediately generated by the counsellor. Referrals generated from disposition rounds were also given heightened priority, with the aim of offering an appointment within 2 weeks from the referral date. To avoid increased financial and human resource recruitment to facilitate the anticipated increase in volume, all first appointment time slots were reduced from 1 hr to 45 min and a standardized dictation template developed to minimize time allocated to documentation. • No collaborative care model (prior May 2016) All patients with a new pathologic diagnosis of EOC are discussed at weekly gynaecologic oncology disposition rounds, previously attended by staff gynaecologic oncologists and gynaecologic pathologists only. Referral of eligible patients for genetic counselling was at the discretion of the staff gynaecologic oncologist and was triaged to be seen within 6 months by MMGS, the sole provider of genetic counselling and testing within the Maritime provinces.
Duration of follow-up	Not applicable
Sources of funding	The project was supported by a grant from AstraZeneca Canada Inc.
Sample size	n=301 in Pre-model; n=85 in Post-model

Study arms

Collaborative care model (N = 85)

Pre-collaborative care model (N = 301)

Outcomes

Time from diagnosis to referral

Outcome	Collaborative care model, N = 85	Pre-collaborative care model, N = 301
Time from diagnosis to referral: median (Units not reported, days?) Custom value	36	110

Time from diagnosis to referral: median - Polarity - Lower values are better

Time from referral to first appointment

Outcome	Collaborative care model, N = 85	Pre-collaborative care model, N = 301
Time from referral to first appointment: median (Units not reported, days?) Custom value	19	73

Time from referral to first appointment: median - Polarity - Lower values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(incomplete adjustment for confounders)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(More women in the Collaborative model group were younger when compared to the Pre-Collaborative model, 66% vs 29% aged <60 years)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

1

2 **Yoon, 2022**

Bibliographic Reference Yoon, Sook-Yee; Wong, Siu Wan; Lim, Joanna; Ahmad, Syuhada; Mariapun, Shivaani; Padmanabhan, Heamanthaa; Hassan, Nur Tiara; Lau, Shao Yan; Ch'ng, Gaik-Siew; Haniffa, Muzhirah; Ong, Winnie P; Rethanavelu, Kavitha; Moey, Lip Hen; Keng, Wee Teik; Omar, Jamil; Mohd Abas, Mohd Norazam; Yong, Chee Meng; Ramasamy, Vickneswaren; Md Noor, Mohd Rushdan; Aliyas, Ismail; Lim, Michael C K; Suberamaniam, Anuradha; Mat Adenan, Noor Azmi; Ahmad, Zatul Akmar; Ho, Gwo Fuang;

Abdul Malik, Rozita; Subramaniam, Suguna; Khoo, Boom Ping; Raja, Arivendran; Chin, Yeung Sing; Sim, Wee Wee; Teh, Beng Hock; Kho, Swee Kiong; Ong, Eunice S E; Voon, Pei Jye; Ismail, Ghazali; Lee, Chui Ling; Abdullah, Badrul Zaman; Loo, Kwong Sheng; Lim, Chun Sen; Lee, Saw Joo; Lim, Keng Joo Lim; Shafiee, Mohamad Nasir; Ismail, Fuad; Latiff, Zarina Abdul; Ismail, Mohd Pazudin; Mohamed Jamli, Mohamad Faiz; Kumarasamy, Suresh; Leong, Kin Wah; Low, John; Md Yusof, Mastura; Ahmad Mustafa, Ahmad Muzamir; Mat Ali, Nor Huda; Makanjang, Mary; Tayib, Shahila; Cheah, Nellie; Lim, Boon Kiong; Fong, Chee Kin; Foo, Yoke Ching; Mellor Abdullah, Matin; Tan, Teck Sin; Chow, Doris S Y; Ho, Kean Fatt; Raman, Rakesh; Radzi, Ahmad; Deniel, Azura; Teoh, Daren C Y; Ang, Soo Fan; Joseph, Joseph K; Ng, Paul Hock Oon; Tho, Lye-Mun; Ahmad, Azura Rozila; Muin, Ileena; Bleiker, Eveline; George, Angela; Thong, Meow-Keong; Woo, Yin Ling; Teo, Soo Hwang; Oncologist-led BRCA counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes.; Journal of medical genetics; 2022; vol. 59 (no. 3); 220-229

Study details

Country/ies where study was carried out	Malaysia
Study type	Prospective cohort study
Study dates	Between August 2016 and October 2019
Inclusion criteria	Women: • aged 21-75 years • newly diagnosed with non-mucinous ovarian, fallopian tube or primary peritoneal cancer
Exclusion criteria	
Patient characteristics	N=790 women with newly diagnosed with non-mucinous ovarian, fallopian tube or primary peritoneal cancer. **Gender:** women **Age (years, mean (SD)):** 52.4 (10.8) **Ethnicity (n):** Malay 362 (45.8%), Chinese 290 (36.7%), Indian 73 (9.2%), Indigenous 44 (5.6%), other 21 (2.7%)

	Socioeconomic and geographical factors (n): Education: primary or less 156 (22%), secondary 339 (48.2%), tertiary 208 (29.6%), unknown 87 **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not applicable **Non-binary people:** not reported
Intervention(s)/control	• Mainstreaming Genetic Counselling Oncologist-led genetic counselling. Oncologists defined as medical and clinical oncologists, surgical oncologists (gynaecologists) or gynaecologists with training in oncology. Oncologists were offered the choice to be trained for mainstreaming or to refer their patients to the genetics team as per the standard genetics referral pathway. All clinicians attended a workshop and completed the online training module established by the Royal Marsden Hospital, UK. In the mainstreaming arm, the pre-test counselling and negative test results were provided by the oncologist. All patients with pathogenic or likely pathogenic variants (analysed together as pathogenic variants), or variants of uncertain significance (VUS) were provided with test results by either the clinical geneticist or the genetic counsellor. • Standard genetics referral pathway Pre-test and post-test counselling were provided by the clinical geneticist or genetic counsellor.
Duration of follow-up	Not applicable
Sources of funding	Yayasan Sime Darby, Yayasan PETRONAS, Khind Starfish Foundation, AstraZeneca External Investigator Grant.
Sample size	N=790 but analysed N=512 (those who completed the questionnaires)

Study arms

Mainstreaming genetic counselling (N = 435)

Standard genetics referral pathway (N = 77)

Outcomes

Psychosocial impact

Outcome	Mainstreaming genetic counselling, N = 234	Standard genetics referral pathway, N = 41
Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC): post-test overall (ORs from logistic regression analysis adjusting for education level and language spoken at interviews) ref; reference; OR (CI 95%): odds ratio with 95% confidence interval Custom value	Reference	OR 0.9 (0.5 to 1.6)

Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC): post-test overall - Polarity - Lower values are better
Assessed using the Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC: 6 domains containing 26 questions, scored 1–4). Patients were considered to have a problem if one or more items scored ≥3)

Satisfaction with genetic counselling

Outcome	Mainstreaming genetic counselling, N = 435	Standard genetics referral pathway, N = 77
Genetic Counselling Satisfaction Scale (GCSS), post-test: adjusted median (IQR) (median adjusted for education level and language spoken at interviews) IQR: interquartile range Custom value	24 (23 to 27)	24 (23.5 to 28)

Genetic Counselling Satisfaction Scale (GCSS), post-test: adjusted median (IQR) - Polarity - Higher values are better

Assessed using Genetic Counselling Satisfaction Scale (GCSS: composite score from a 6-item GCSS scale. Scores range from 6-30 and scores ≥24 indicate good satisfaction level)

Psychosocial impact

Outcome	Mainstreaming genetic counselling, N = 435	Standard genetics referral pathway, N = 77
Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC): post-test overall (a problem with at least one of the domains) No of events	n = 234; % = 54	n = 41; % = 53

Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC): post-test overall (a problem with at least one of the domains) - Polarity - Lower values are better

Critical appraisal – NGA Critical appraisal - ROBINS I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(although logistic regression analysis took into account baseline confounders such as education level and language spoken at interview/consent, it did not account for other baseline differences, for example ethnicity (mainstreaming pathway group included 50.8% Malay and 31.2% Chinese participants whereas the standard genetics referral pathway group included 15.3% Malay and 70.3% Chinese participants)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended	Low

Section	Question	Answer
	interventions	
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Participants who did not complete the questionnaires were older at diagnosis (mean age 54.5±10.9 vs 51.2±10.6, p=<0.01) and were less educated (30% vs 19% with less than primary school education)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

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Appendix E Forest plots

Forest plots for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

Women with ovarian cancer

Table 4: Evidence profile for comparison between mainstream germline genetic testing program and cancer genetic service in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mainstream genetic testing program	Cancer genetic service	Relative (95% CI)	Absolute		
Time from blood collection to report (days): reported as mean (range) (Better indicated by lower values)												
Ip 2022	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=138 62.6 (11-153)	n=69 55.6 (7-153)	-	Mean 7 days longer (CI not reported)[3]	LOW	IMPORTANT

CI: confidence interval
1 No adjustment for potential confounders; no description of the control group
2 Optimal information size for imprecision: N<400
3 Not reported if there was a statistical difference between the two groups in terms of time from blood collection to report

Table 5: Evidence profile for comparison between mainstreaming genetic counselling and standard genetics referral pathway in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mainstreaming genetic counselling	Standard genetics referral pathway	Relative (95% CI)	Absolute		
Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC): post-test overall												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mainstreaming genetic counselling	Standard genetics referral pathway	Relative (95% CI)	Absolute		
Yoon 2022	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/234 (0%)	0/41 (0%)	OR 0.9 (0.5 to 1.6)*	No difference	VERY LOW	CRITICAL
Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC): post-test overall (a problem with at least one of the domains)												
Yoon 2022	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	234/435 (53.8%)	41/77 (53.2%)	RR 1.01 (0.81 to 1.27)	2 more per 1000 (from 53 fewer to 59 more)	LOW	CRITICAL
Genetic Counselling Satisfaction Scale (GCSS), post-test: reported as adjusted median (IQR) (Better indicated by lower values); median adjusted for education level and language spoken at interviews												
Yoon 2022	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	n=435 24 (23 to 27)	n=77 24 (23.5 to 28)	-	No diffference[4]	MODERATE	CRITICAL

CI: confidence interval; OR: odds ratio; RR: relative risk PAHC: assessed using the Psychosocial Aspects of Hereditary Cancer Questionnaire (PAHC: 6 domains containing 26 questions, scored 1–4. Patients were considered to have a problem if one or more items scored ≥3) GCSS: assessed using Genetic Counselling Satisfaction Scale (GCSS: composite score from a 6-item GCSS scale. Scores range from 6-30 and scores ≥24 indicate good satisfaction level)

** OR as reported in the paper, reference being mainstreaming genetic counselling; no raw data reported*

1 Although logistic regression analysis took into account baseline confounders such as education level and language spoken at interview/consent, it did not account for other baseline differences, for example ethnicity (mainstreaming pathway group included 50.8% Malay and 31.2% Chinese participants whereas the standard genetics referral pathway group included 15.3% Malay and 70.3% Chinese participants. Participants who did not complete the questionnaires were older at diagnosis (mean age 54.5±10.9 vs 51.2±10.6, p=<0.01) and were less educated (30% vs 19% with less than primary school education

2 95% CI crosses 2 default MIDs

3 95% CI crosses 1 default MID

4 Reported that there was no statistical difference between the two groups in terms of genetic counselling satisfaction (p=1.00)

Table 6: Evidence profile for comparison between streamlined pre-test genetic education and genetic panel testing and current standard counselling and testing in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Streamlined pre-test genetic education and genetic panel testing	Current standard counselling and testing	Relative (95% CI)	Absolute		
Time from diagnosis to genetic test result (days): reported as median (Better indicated by lower values)												
Powell 2020	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 31	n=101 43	-	Median 12 lower[3]	VERY LOW	IMPORTANT
Time from diagnosis to blood draw (days): reported as median (Better indicated by lower values)												
Powell 2020	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=40 18.5	n=101 25.5		Median 7 lower[3]	VERY LOW	IMPORTANT
Patient satisfaction with genetic testing: distress (Better indicated by lower values)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	37	40	-	MD 1.3 lower (3.9 lower to 1.3 higher)	LOW	CRITICAL
Patient satisfaction with genetic testing: uncertainty (Better indicated by lower values)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	37	40	-	MD 0.1 lower (3.38 lower to 3.18 higher)	VERY LOW	CRITICAL
Patient satisfaction with genetic testing: positive experience (Better indicated by lower values)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	37	40	-	MD 1.4 higher (0.98 lower to 3.78 higher)	LOW	CRITICAL
Patient satisfaction with genetic testing: I felt satisfied with time for discussion (strongly agree)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	21/37 (56.8%)	24/40 (60%)	RR 0.95 (0.65 to 1.38)	30 fewer per 1000 (from 210 fewer to 228 more)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Streamlined pre-test genetic education and genetic panel testing	Current standard counselling and testing	Relative (95% CI)	Absolute		
Patient satisfaction with genetic testing: I felt adequately informed (strongly agree)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	20/37 (54.1%)	22/40 (55%)	RR 0.98 (0.65 to 1.48)	11 fewer per 1000 (from 193 fewer to 264 more)	VERY LOW	CRITICAL
Patient satisfaction with genetic testing: I had sufficient time to think (strongly agree)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	19/37 (51.4%)	23/40 (57.5%)	RR 0.89 (0.59 to 1.35)	63 fewer per 1000 (from 236 fewer to 201 more)	VERY LOW	CRITICAL
Patient satisfaction with genetic testing: I was happy with the process (strongly agree)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	22/37 (59.5%)	26/40 (65%)	RR 0.91 (0.64 to 1.30)	58 fewer per 1000 (from 234 fewer to 195 more)	VERY LOW	CRITICAL
Patient satisfaction with genetic testing: the genetic counselling provided was adequate (strongly agree)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	20/37 (54.1%)	22/40 (55%)	RR 0.98 (0.65 to 1.48)	11 fewer per 1000 (from 193 fewer to 264 more)	VERY LOW	CRITICAL
Patient satisfaction with genetic testing: I am pleased I had the genetic test (strongly agree)												
Powell 2020	observational studies	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	25/37 (67.6%)	29/40 (72.5%)	RR 0.93 (0.69 to 1.25)	51 fewer per 1000 (from 225 fewer to 181 more)	LOW	CRITICAL

CI: confidence interval; MD: mean difference; RR: relative risk; patient satisfaction measured using the Multidimensional Impact of Cancer Risk Assessment Questionnaire (a 25-question assessment of genetic testing concerns) and 6 additional questions adapted from the George et al 2016

1 No adjustment for potential confounders

2 Optimal information size for imprecision: N<200

3 Not reported if there was a statistical difference between the two groups in terms of time from diagnosis to genetic test result or to blood draw

4 No adjustment for potential confounders; patient satisfaction survey was completed by 93% of those in the streamlined testing group and by 40% of those in the standard testing group only

5 95% CI crosses 1 MID (0.5x control group SD = 6.9)

6 95% CI crosses 2 MIDs (0.5x control group SD = 6)

7 95% CI crosses 1 MID (0.5x control group SD = 6)

8 95% CI crosses 1 default MID
9 95% CI crosses 2 default MIDs

Table 7: Evidence profile for comparison between gynaecologic oncologist-initiated genetic testing model and traditional genetics referral-based program in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Gynaecologic oncologist-initiated genetic testing model	Traditional genetics referral-based program	Relative (95% CI)	Absolute		
Time from diagnosis to genetic testing (days): reported as median (range) (Better indicated by lower values)												
Piedimonte 2020	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=44 median (range) 40 (8-175)	n=108 median (range) 154 (4-848)	-	Median 114 lower (range not reported)[3]	VERY LOW	IMPORTANT
Delay between testing and result (days): reported as median (range) (Better indicated by lower values)												
Piedimonte 2020	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=44 median (range) 8 (8-48)	n=108 median (range) 28.5 (7-271)	-	Median 20.5 lower (range not reported)[3]	VERY LOW	IMPORTANT
Time between blood sample acquisition and return of *BRCA* result to the treating oncologist (days): reported as mean (range) (Better indicated by lower values)												
Rumford 2020	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	N not reported 20.6 (11-42)	N not reported 148.2 (98-175)	-	MD 127.6 lower[6]	VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference: NR: not reported
1 No adjustment for potential confounders
2 Optimal information size for imprecision: N<200
3 Reported that there was a significant difference between the two groups in terms of time from diagnosis to genetic testing (p<0.01) and delay between testing and result (p=0.002)
4 No adjustment for potential confounders; no description of the control group; the number of participants in each group is not clear
5 Not possible to make a judgement on imprecision as no standard deviation reported and therefore no mean difference calculated
6 Not reported if there was a significant difference between the two groups in terms of time between blood sample acquisition and return of the result to the treating oncologist

Table 8: Evidence profile for comparison between addition of an embedded genetic counsellor in the medical and gynaecologic oncology clinic and standard clinic in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Addition of an embedded genetic counsellor in the medical/ gynaecologic oncology clinic	Standard clinic	Relative (95% CI)	Absolute		
Time from initial consultation to genetic counselling (days): reported as median (Better indicated by lower values)												
Rana 2021	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=119 40	n=135 107	-	Median 67 lower[3]	LOW	IMPORTANT
Proportion of patients seen for ovarian cancer treatment who received genetic testing within 3 months of their initial visit												
Rana 2021	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	72/119 (60.5%)	45/135 (33.3%)	RR 1.82 (1.37 to 2.40)	273 more per 1000 (from 123 more to 467 more)	MODERATE	IMPORTANT

CI: confidence interval; RR: relative risk
1 No adjustment for potential confounders; no description of the control group
2 Optimal information size for imprecision: N<400
3 Reported that there was a significant difference between the two groups in terms of time from initial consultation to genetic counselling (p<0.01)

Table 9: Evidence profile for comparison between genetics embedded model and no genetic embedded model service in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Genetics embedded model (incorporates cancer genetic counsellor on-site in the clinic)	No genetics-embedded model of service	Relative (95% CI)	Absolute		
Time from referral to scheduling in genetics (months): reported as mean (Better indicated by lower values)												
Senter 2017	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	n=336 0.79	n=401 3.92	-	Mean 3.13 lower[3]	MODERATE	IMPORTANT
Time from referral to completion of genetics consultation (months): reported as mean (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Genetics embedded model (incorporates cancer genetic counsellor on-site in the clinic)	No genetics-embedded model of service	Relative (95% CI)	Absolute		
Senter 2017	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	n=336 1.67	n=401 2.52	-	Mean 0.85 lower[3]	MODERATE	IMPORTANT

CI: confidence interval; a "scheduled" appointment defined as a documented appointment in the electronic health records on the clinical genetics schedule; "completion" of counselling defined as a closed encounter with the genetic counsellor
1 No adjustment for potential confounders
2 Optimal information size for imprecision: N>400
3 Reported that there was a significant difference between the groups in terms of time from referral to scheduling in genetics (p<0.00001) and to completion of genetics consultation (p<0.01)

Table 10: Evidence profile for comparison between collaborative care model and no collaborative care model in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Collaborative care model (genetic counsellor integrated into tumour board rounds)	No collaborative care model	Relative (95% CI)	Absolute		
Time from diagnosis to referral (units not reported, days?): reported as median (Better indicated by lower values)												
Warias 2021	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=85 36	n=301 110	-	Median 74 lower[3]	LOW	IMPORTANT
Time from referral to first appointment (units not reported, days?): reported as median (Better indicated by lower values)												
Warias 2021	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=85 19	n=301 73	-	Median 54 lower[3]	LOW	IMPORTANT

CI: confidence interval; MD: mean difference.
1 No adjustment for potential confounders; More women in the intervention group were younger when compared to the comparison group 66% vs 29% aged <60 years
2 Optimal information size for imprecision: N<400
3 Reported that there was a significant difference between the groups in terms of time from diagnosis to referral (p<0.01) and to first appointment (p<0.01)

Table 11: Evidence profile for comparison between reflex *BRCA1/2* tumour testing and no reflex *BRCA1/2* tumour testing in women with ovarian cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reflex *BRCA1/2* tumour testing	No Reflex BRCA1/2 tumour testing	Relative (95% CI)	Absolute		
Time to referral for genetic counselling (days): reported as median (95% CI) (Better indicated by lower values)												
McCuaig 2020	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	n=94 33 (29.05-36.96)	n=81 59 (27.87-90.13)	-	Median 26.00 days lower (56.91 lower to 4.91 higher)[3]	VERY LOW	IMPORTANT

CI: confidence interval
1 No adjustment for potential confounders
2 Optimal information size for imprecision: N<200
3 Reported that there was a statistical difference between the two groups in terms of time to referral for counselling (p=0.04)

Women with breast cancer

Table 12: Evidence profile for comparison between specialist, nurse-led mainstreaming cancer genetics (MCG) service and pre-MCG service in women with breast cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Specialist, nurse-led mainstreaming cancer genetics (MCG) service	Pre-MCG service	Relative (95% CI)	Absolute		
Time from testing until genetic test result (days): reported as mean (Better indicated by lower values)												
Scott 2020	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	n=290 35.8	- 122 to 183	-	-[3]	VERY LOW	IMPORTANT

CI: confidence interval
1 No adjustment for potential confounders; the total and sociodemographic characteristics of the control group not clear
2 Optimal information size for imprecision: N<400
3 Not reported if there was a significant difference between the two groups in terms of time from testing until genetic test result

BRCA1/2 carriers

Table 13: Evidence profile for comparison between multidisciplinary one-stop follow-up clinic and no multidisciplinary one-stop follow-up clinic in *BRCA1/2* carriers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multidisciplinary one-stop follow-up clinic	No Multidisciplinary one-stop follow-up clinic	Relative (95% CI)	Absolute		
Recruitment to trials (UKFOCCS trial)												
Pichert 2010	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/46 (47.8%)	5/85 (5.8%)	RR 8.13 (3.30, 20.04)	419 more per 1000 (from 135 more to 1000 more)	MODERATE	IMPORTANT
Recruitment to trials (EMBRACE trial)												
Pichert 2010	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	101/126 (80.2%)	46/172 (26.7%)	RR 3.00 (2.31, 3.90)	535 more per 1000 (from 350 more to 776 more)	MODERATE	IMPORTANT

CI: confidence interval; RR: relative risk
1 No adjustment for potential confounders; no description of the control group

Appendix G Economic evidence study selection

Study selection for: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

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: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

Excluded effectiveness/ service delivery studies

Table 14: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Antill, Y.C.; Shanahan, M.; Phillips, K.-A. (2005) The integrated, multidisciplinary clinic: A new model for the ongoing management of women at high genetic risk for breast and ovarian cancer. Cancer Forum 29(2): 107-110	Comparator in study does not match that specified in this review protocol
Azzollini, J., Vingiani, A., Agnelli, L. et al. (2022) Management of BRCA Tumour Testing in an Integrated Molecular Tumour Board Multidisciplinary Model. Frontiers in Oncology 12: 857515	Outcomes in study do not match those specified in this review protocol
Dhivya, Chandrasekaran, Monika, Sobocan, Oleg, Blyuss et al. (2021) Implementation of Multigene Germline and Parallel Somatic Genetic Testing in Epithelial Ovarian Cancer: SIGNPOST Study. Cancers (Basel) Aug 27;13(17):4344	Comparator in study does not match that specified in this review protocol
Colombo, Nicoletta, Huang, Gloria, Scambia, Giovanni et al. (2018) Evaluation of a Streamlined Oncologist-Led BRCA Mutation Testing and Counseling Model for Patients With Ovarian Cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36(13): 1300-1307	Comparator in study does not match that specified in this review protocol
D'Andrea, Elvira, Marzuillo, Carolina, De Vito, Corrado et al. (2016) Which BRCA genetic testing programs are ready for implementation in health care? A systematic review of economic evaluations. Genetics in medicine: official journal of the American College of Medical Genetics 18(12): 1171-1180	Intervention in study does not match that specified in this review protocol
DeFrancesco, M.S., Waldman, R.N., Pearlstone, M.M. et al. (2018) Hereditary cancer risk assessment and genetic testing in the community-practice setting. Obstetrics and Gynecology 132(5): 1121-1129	Comparator in study does not match that specified in this review protocol
Drescher, Charles W, Beatty, J David, Resta, Robert et al. (2016) The effect of referral for genetic counseling on genetic testing and surgical prevention in women at high risk for ovarian cancer: Results from a randomized controlled trial. Cancer 122(22): 3509-3518	Comparator in study does not match that specified in this review protocol
Evans, D Gareth, Astley, Susan, Stavrinos, Paula et al. (2016) Improvement in risk prediction, early detection and prevention of breast cancer in the NHS Breast Screening Programme and family history clinics: a dual cohort study	Intervention in study does not match that specified in this review protocol
Firth, Clare, Jacobs, Christine, Evison, Margaret et al. (2011) Novel one-stop multidisciplinary follow-up clinic for BRCA1/2 carriers: patient satisfaction and decision making. Psychooncology 20(12): 1301-1308	Comparator in study does not match that specified in this review protocol
Flaum N, Morgan RD, Burghel GJ et al. (2020) Mainstreaming germline BRCA1/2 testing in non-mucinous epithelial ovarian cancer in the North West of England. European journal of human genetics: EJHG vol. 28 (no. 11)	Outcomes in study do not match those specified in this review protocol
Frey, Melissa K, Lee, Sarah S, Gerber, Deanna et al. (2020) Facilitated referral pathway for genetic testing at the time of ovarian cancer	Comparator in study does not match that specified in

Study	Reason for exclusion
diagnosis: uptake of genetic counseling and testing and impact on patient-reported stress, anxiety and depression. Gynecologic oncology 157(1): 280-286	this review protocol
George, Angela, Riddell, Daniel, Seal, Sheila et al. (2016) Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. Scientific reports 6: 29506	Comparator in study does not match that specified in this review protocol
Helsper, Charles W, Van Vliet, Liesbeth M, Velthuizen, Mary E et al. (2018) Identifying patients with a history of ovarian cancer for referral for genetic counselling: non-randomised comparison of two case-finding strategies in primary care. The British journal of general practice: the journal of the Royal College of General Practitioners 68(676): e750-e756	Outcomes in study do not match those specified in this review protocol
Interrante, Mary K, Segal, Hannah, Peshkin, Beth N et al. (2017) Randomized Noninferiority Trial of Telephone vs In-Person Genetic Counseling for Hereditary Breast and Ovarian Cancer: A 12-Month Follow-Up. JNCI cancer spectrum 1(1): pkx002	Intervention in study does not match that specified in this review protocol
Kentwell, Maira, Dow, Eryn, Antill, Yoland et al. (2017) Mainstreaming cancer genetics: A model integrating germline BRCA testing into routine ovarian cancer clinics. Gynecologic oncology 145(1): 130-136	Comparator in study does not match that specified in this review protocol
Lin, Jenny, Sharaf, Ravi N, Saganty, Rachel et al. (2021) Achieving universal genetic assessment for women with ovarian cancer: Are we there yet? A systematic review and meta-analysis. Gynecologic oncology 162(2): 506-516	Systematic review used as source of primary studies
Moya-Alarcon, Carlota, Gonzalez-Dominguez, Almudena, Simon, Susana et al. (2019) Cost-utility analysis of germline BRCA1/2 testing in women with high-grade epithelial ovarian cancer in Spain. Clinical & translational oncology: official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 21(8): 1076-1084	Comparator in study does not match that specified in this review protocol
Petelin, Lara, Trainer, Alison H, Mitchell, Gillian et al. (2018) Cost-effectiveness and comparative effectiveness of cancer risk management strategies in BRCA1/2 mutation carriers: a systematic review. Genetics in medicine: official journal of the American College of Medical Genetics 20(10): 1145-1156	Intervention in study does not match that specified in this review protocol
Petzel, Sue V, Vogel, Rachel Isaksson, Bensend, Tracy et al. (2013) Genetic risk assessment for women with epithelial ovarian cancer: referral patterns and outcomes in a university gynecologic oncology clinic. Journal of genetic counseling 22(5): 662-73	Intervention in study does not match that specified in this review protocol
Powell, C Bethan, Littell, Ramey, Hoodfar, Elizabeth et al. (2013) Does the diagnosis of breast or ovarian cancer trigger referral to genetic counseling?. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 23(3): 431-6	Comparator in study does not match that specified in this review protocol
Rahman, Belinda, Lanceley, Anne, Kristeleit, Rebecca S et al. (2019) Mainstreamed genetic testing for women with ovarian cancer: first-year experience. Journal of medical genetics 56(3): 195-198	Comparator in study does not match that specified in this review protocol
Ricci, Maria Teresa, Sciallero, Stefania, Mammoliti, Serafina et al. (2015) Referral of Ovarian Cancer Patients for Genetic Counselling by Oncologists: Need for Improvement. Public health genomics 18(4): 225-32	Comparator in study does not match that specified in this review protocol
Ricker, C., Lagos, V., Feldman, N. et al. (2006) If we build it... will they come? - Establishing a cancer genetics services clinic for an underserved predominantly latina cohort. Journal of Genetic Counseling 15(6): 505-514	Intervention in study does not match that specified in this review protocol
Smallwood, K G, Crockett, S, Huang, V et al. (2022) Changing patterns of referral into a family history clinic and detection of ovarian cancer: a retrospective 10-year review. Journal of obstetrics and gynaecology:	Intervention in study does not match that specified in this review protocol

Study	Reason for exclusion
the journal of the Institute of Obstetrics and Gynaecology: 1-7	
Swanson, Casey L, Kumar, Amanika, Maharaj, Joy M et al. (2018) Increasing genetic counseling referral rates through bundled interventions after ovarian cancer diagnosis. Gynecologic oncology 149(1): 121-126	Outcomes in study do not match those specified in this review protocol
Wood, N J, Munot, S, Sheridan, E et al. (2008) Does a "one-stop" gynecology screening clinic for women in hereditary nonpolyposis colorectal cancer families have an impact on their psychological morbidity and perception of health? International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 18(2): 279-84	Intervention in study does not match that specified in this review protocol

Excluded economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the most effective configuration of services for referral, risk assessment and risk management for women at increased risk of ovarian cancer (including fertility, menopause and psychological support services)?

No research recommendations were made for this review question.