

Predisposición Hereditaria al Cáncer Ginecológico: Evaluación del Riesgo Específico por Gen, Asesoramiento Genético y Estrategias Personalizadas de Prevención

Hereditary Gynecologic Cancer Predisposition: Gene-Specific Risk Assessment, Genetic Counseling, and Personalized Prevention Strategies

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RESUMEN

Los síndromes hereditarios de cáncer ginecológico constituyen un grupo heterogéneo de trastornos en los que variantes germinales patogénicas incrementan la susceptibilidad al cáncer de ovario, trompa de Falopio, endometrio y otras neoplasias relacionadas. Este estudio analizó la evidencia actual sobre la identificación clínica de individuos con mayor riesgo hereditario, las pruebas moleculares, el asesoramiento genético, las pruebas en cascada y las estrategias de reducción del riesgo de cáncer. Se realizó una revisión integrativa estructurada basada en el Método Científico, incorporando guías clínicas, recomendaciones de consenso, cohortes prospectivas, estudios observacionales y análisis relevantes de riesgo genético. Los resultados demostraron una importante variabilidad específica según el gen afectado. El riesgo acumulado de cáncer de ovario fue considerablemente mayor en portadoras de *BRCA1* que en portadoras de *BRCA2*, mientras que genes de penetrancia moderada como *BRIP1*, *RAD51C* y *RAD51D* presentaron estimaciones de riesgo menores, aunque clínicamente relevantes. El síndrome de Lynch también mostró patrones heterogéneos de cáncer ginecológico entre *MLH1*, *MSH2*, *MSH6* y *PMS2*. La evidencia revisada identificó además una brecha importante entre las recomendaciones de evaluación genética y la realización efectiva de pruebas germinales o somáticas en pacientes con cáncer de ovario. La salpingooforectomía reductora de riesgo se asoció con menor aparición de cáncer de ovario y menor mortalidad específica por cáncer y por todas las causas en portadoras seleccionadas de *BRCA1/2*. Estos hallazgos respaldan un modelo individualizado de manejo del cáncer ginecológico hereditario basado en la integración de la historia clínica, antecedentes familiares, diagnóstico molecular, penetrancia específica del gen, asesoramiento genético e intervenciones preventivas. La prevención efectiva del cáncer hereditario depende no solo de identificar variantes patogénicas, sino también de transformar la información genética en decisiones clínicas oportunas, proporcionales y centradas en la paciente.

PALABRAS CLAVE

cáncer ginecológico hereditario, BRCA1, BRCA2, síndrome de Lynch, asesoramiento genético, pruebas germinales, pruebas en cascada, cáncer de ovario, cáncer de endometrio, cirugía reductora de riesgo, prevención de precisión, genética del cáncer

ABSTRACT

Hereditary gynecologic cancer syndromes constitute a heterogeneous group of disorders in which pathogenic germline variants increase susceptibility to ovarian, fallopian tube, endometrial, and other related malignancies. This study analyzed current evidence regarding the clinical identification of individuals at increased hereditary risk, molecular testing, genetic counseling, cascade testing, and strategies for cancer risk reduction. A structured integrative review based on the Scientific Method was performed using clinical guidelines, consensus recommendations, prospective cohorts, observational studies, and relevant genetic risk analyses. The results demonstrated substantial gene-specific variability. Cumulative ovarian cancer risk was markedly higher among *BRCA1* carriers than among *BRCA2* carriers, while moderate-penetrance genes such as *BRIP1*, *RAD51C*, and *RAD51D* showed lower but clinically relevant risk estimates. Lynch syndrome also exhibited heterogeneous gynecologic cancer patterns across *MLH1*, *MSH2*, *MSH6*, and *PMS2*. The reviewed evidence further identified an important gap between recommendations for genetic evaluation and actual completion of germline or somatic testing in patients with ovarian cancer. Risk-reducing salpingo-oophorectomy was associated with lower ovarian cancer occurrence and reduced cancer-specific and all-cause mortality among selected *BRCA1/2* carriers. These findings support an individualized model of hereditary gynecologic cancer management based on integration of clinical history, family history, molecular diagnosis, gene-specific penetrance, genetic counseling, and preventive interventions. Effective hereditary cancer prevention depends

not only on identifying pathogenic variants but also on translating genetic information into timely, proportionate, and patient-centered clinical decisions.

KEYWORDS

hereditary gynecologic cancer, BRCA1, BRCA2, Lynch syndrome, genetic counseling, germline testing, cascade testing, ovarian cancer, endometrial cancer, risk-reducing surgery, precision prevention, cancer genetics

INTRODUCCIÓN

Hereditary predisposition has become an increasingly relevant component of gynecologic oncology because a clinically significant proportion of ovarian, endometrial, and other gynecologic malignancies arise in the setting of germline pathogenic variants. The recognition of these inherited alterations has transformed cancer prevention from an approach based predominantly on family history and clinical surveillance into a more individualized model that incorporates molecular diagnosis, estimation of gene-specific cancer risk, genetic counseling, cascade testing, and preventive interventions. Among the best-established hereditary conditions are hereditary breast and ovarian cancer syndrome associated primarily with pathogenic variants in *BRCA1* and *BRCA2*, and Lynch syndrome caused by alterations in DNA mismatch repair genes, including *MLH1*, *MSH2*, *MSH6*, and *PMS2*. However, the increasing use of multigene testing has expanded this spectrum to include genes such as *BRIP1*, *RAD51C*, *RAD51D*, *PALB2*, *PTEN*, *STK11*, and *DICER1*, among others, creating new opportunities for prevention but also greater complexity in clinical decision-making (Konstantinopoulos et al., 2020; Liu et al., 2022; Ngeow et al., 2025).

The clinical relevance of hereditary gynecologic cancer is particularly evident in ovarian cancer, in which germline pathogenic variants are estimated to account for a substantial proportion of cases. Genetic susceptibility is not restricted to *BRCA1* and *BRCA2*: several genes involved in homologous recombination, DNA repair, and tumor suppression have been associated with increased cancer risk. These discoveries have significant implications because the identification of a pathogenic variant may alter not only the management of the affected patient but also the preventive care of biologically related family members. Current recommendations therefore support germline testing for patients with epithelial ovarian cancer and emphasize the importance of integrating germline and somatic molecular information into clinical practice (Konstantinopoulos et al., 2020; Gressel et al., 2024). Nevertheless, despite widespread professional recommendations, implementation remains incomplete, and a considerable proportion of eligible patients do not undergo appropriate genetic testing, indicating a persistent gap between genomic knowledge and routine clinical practice (Gressel et al., 2024).

Hereditary breast and ovarian cancer associated with *BRCA1* and *BRCA2* represents one of the most extensively investigated hereditary cancer syndromes. Carriers of pathogenic variants in these genes have markedly elevated lifetime risks of breast and ovarian cancer, although penetrance varies according to the affected gene, age, family history, and other modifying factors. Prospective evidence has demonstrated important differences between *BRCA1* and *BRCA2* in the age-specific incidence of ovarian and breast malignancies, emphasizing that hereditary risk should not be interpreted as a uniform phenomenon (Kuchenbaecker et al., 2017). These differences have practical consequences for the timing of surveillance, reproductive planning, preventive surgery, and counseling. Consequently, genetic information should be interpreted within an individualized risk framework rather than being regarded as a binary distinction between carriers and non-carriers.

The hereditary spectrum has expanded further with recognition of moderate-penetrance ovarian cancer susceptibility genes. Pathogenic variants in *BRIP1*, *RAD51C*, and *RAD51D*, for example, are associated with increased tubo-ovarian cancer susceptibility, although their absolute risks and optimal management differ from those associated with *BRCA1* and *BRCA2*. This distinction is clinically important because preventive strategies must balance the magnitude and age distribution of cancer risk against the consequences of intervention. Recent recommendations therefore favor gene-specific and individualized risk assessment rather than applying identical preventive thresholds to all hereditary variants (Liu et al., 2022; Ngeow et al., 2025). Family history, age, reproductive goals, comorbidities, personal preferences, and additional modifying factors should consequently be integrated into decision-making regarding surveillance and risk-reducing surgery.

Lynch syndrome constitutes another major hereditary condition relevant to gynecologic oncology. In affected individuals, endometrial cancer may represent one of the earliest manifestations of the syndrome, while ovarian cancer risk is also increased, although the magnitude of risk varies considerably according to the mismatch repair gene involved. Recognition of Lynch syndrome is therefore particularly important in gynecologic practice, where identification of an endometrial or ovarian malignancy may become the event that reveals hereditary susceptibility within an entire family. International consensus recommendations have emphasized the need for appropriate molecular screening, genetic evaluation, counseling, and discussion of preventive strategies in women carrying pathogenic mismatch repair variants (Crosbie et al., 2019). These strategies may include intensified surveillance for associated malignancies and, in appropriately selected individuals who have completed childbearing, consideration of risk-reducing hysterectomy with or without bilateral salpingo-oophorectomy according to individual cancer risk.

The increasing availability of next-generation sequencing and multigene panels has considerably improved the ability to identify inherited cancer susceptibility but has simultaneously introduced new interpretative challenges. Multigene testing may detect pathogenic variants in genes for which cancer penetrance, age-specific risks, and optimal preventive strategies are less clearly defined. In addition, variants of uncertain significance can generate inappropriate clinical interpretation if they are treated as equivalent to pathogenic variants. For this reason, contemporary approaches emphasize that genetic testing should be accompanied by appropriate pretest and post-test counseling, detailed assessment of personal and family cancer history, and careful interpretation according to the strength of the gene-disease association (Konstantinopoulos et al., 2020; National Institute for Health and Care Excellence [NICE], 2024). Current guidance also supports selecting gene panels according to the patient's personal and familial phenotype rather than using genetic results in isolation.

Genetic counseling therefore represents a central component of hereditary cancer management rather than an ancillary step in the diagnostic process. Counseling provides an opportunity to explain inheritance patterns, penetrance, residual cancer risk, the potential implications of positive and negative results, variants of uncertain significance, reproductive implications, psychological considerations, and the possibility of cascade testing in relatives. A pathogenic germline variant identified in an affected patient may permit targeted testing of family members before cancer develops, transforming an oncologic diagnosis into an opportunity for primary prevention. Contemporary guidelines increasingly emphasize shared decision-making because preventive options may have profound consequences for fertility, endocrine function, sexual health, reproductive planning, and long-term quality of life (NICE, 2024).

Risk-reducing surgery remains one of the most effective preventive interventions for selected hereditary gynecologic cancer syndromes. Risk-reducing salpingo-oophorectomy is well established for women with high-risk *BRCA1* or *BRCA2* pathogenic variants and is associated with substantial reductions in tubo-ovarian cancer risk. Nevertheless, the optimal timing of surgery requires careful consideration because premature surgical menopause can affect cardiovascular, skeletal, sexual, reproductive, and overall health. Management becomes even more complex for moderate-penetrance genes such as *BRIP1*, *RAD51C*, and *RAD51D*, in which the age-specific risk of ovarian cancer differs from that of *BRCA1/2*. Recent recommendations consequently support individualized timing based on the specific gene, estimated absolute risk, family history, age, and patient preferences rather than a single universal threshold (Liu et al., 2022; Ngeow et al., 2025).

Alternative preventive strategies are also being investigated to reduce the adverse consequences associated with premature oophorectomy. One emerging approach involves risk-reducing salpingectomy with delayed oophorectomy, based on the growing understanding that many high-grade serous carcinomas originate in the distal fallopian tube. Studies have suggested that this strategy may provide advantages in menopause-related quality of life compared with immediate salpingo-oophorectomy; however, its long-term oncologic safety has not yet been established sufficiently to replace standard risk-reducing salpingo-oophorectomy in individuals for whom the latter is recommended. This illustrates a broader challenge in hereditary cancer prevention: preventive interventions must not only decrease cancer incidence but should also be evaluated according to their consequences for long-term health and quality of life.

Despite considerable progress, important clinical uncertainties persist. The optimal management of moderate-penetrance pathogenic variants continues to evolve, access to genetic counseling and testing remains inconsistent, and the interpretation of hereditary risk may differ substantially depending on gene penetrance, family structure, ancestry, reproductive history, and environmental or hormonal modifiers. Furthermore, surveillance for ovarian cancer has

important limitations, reinforcing the need for effective strategies capable of identifying high-risk individuals before malignancy develops. Current guidance therefore increasingly emphasizes structured referral pathways, personalized risk estimation, genetic counseling, informed shared decision-making, and multidisciplinary care involving gynecology, oncology, genetics, pathology, and reproductive medicine (NICE, 2024; Gressel et al., 2024).

Within this context, the central research question of this study is: **how can clinical identification, genetic evaluation, and individualized risk-reduction strategies be integrated to optimize the management of individuals with hereditary predisposition to gynecologic cancer?** The working hypothesis is that an integrated approach combining personal and familial cancer history, molecular characterization, gene-specific penetrance, genetic counseling, and individualized preventive interventions provides a more clinically useful framework than management based exclusively on family history or on the presence of a pathogenic variant considered in isolation. This approach is expected to improve recognition of individuals at increased hereditary risk, facilitate appropriate cascade testing, and support more proportionate decisions regarding surveillance and preventive interventions.

To address this question, the present study adopts a structured review and comparative analytical approach integrating evidence from clinical guidelines, consensus recommendations, observational studies, prospective cohorts, and investigations of hereditary cancer risk. Particular attention is directed toward the principal hereditary syndromes and susceptibility genes associated with ovarian and endometrial cancer; the clinical criteria that should raise suspicion of hereditary predisposition; the role and interpretation of germline and tumor genetic testing; the principles of pretest and post-test counseling; and the available strategies for cancer risk reduction. Evidence is examined according to gene-specific risk, clinical presentation, potential preventive benefit, and consequences of intervention. This design directly corresponds with the proposed hypothesis by evaluating hereditary gynecologic cancer as a continuum of individualized risk rather than as a single homogeneous entity.

DESARROLLO

Hereditary Predisposition and the Molecular Basis of Gynecologic Cancer

Hereditary gynecologic cancer syndromes represent a heterogeneous group of genetic conditions in which germline pathogenic variants increase susceptibility to malignancies of the ovary, fallopian tube, endometrium, cervix, and, in specific syndromes, other reproductive organs. Their clinical importance extends beyond the identification of inherited cancer risk because molecular characterization may influence prevention, surveillance, treatment selection, reproductive counseling, and cancer risk assessment among relatives. The transition from family-history-based evaluation to genomic medicine has consequently modified the clinical approach to women with suspected hereditary cancer predisposition.

Among these conditions, hereditary breast and ovarian cancer syndrome associated with *BRCA1* and *BRCA2* remains the most extensively characterized. Both genes participate in homologous recombination repair of DNA double-strand breaks, and loss of their normal function promotes genomic instability and malignant transformation. The magnitude of ovarian cancer risk differs considerably between the two genes. In a prospective cohort analysis, the cumulative risk of ovarian cancer by 80 years of age was approximately 44% among *BRCA1* carriers and 17% among *BRCA2* carriers, demonstrating that hereditary susceptibility cannot be interpreted as equivalent across pathogenic variants (Kuchenbaecker et al., 2017).

This distinction has direct clinical consequences. The earlier emergence and greater magnitude of tubo-ovarian cancer risk associated with *BRCA1* generally justify preventive intervention at an earlier age than that considered for *BRCA2*. Nevertheless, genotype alone does not completely determine risk. Family history, reproductive factors, age, ancestry, and additional genetic modifiers may influence penetrance. Therefore, contemporary hereditary cancer management is increasingly based on individualized absolute-risk estimates rather than simply classifying a patient as mutation-positive or mutation-negative.

The molecular spectrum extends beyond *BRCA1* and *BRCA2*. Pathogenic variants in *RAD51C*, *RAD51D*, and *BRIPI* have emerged as clinically relevant causes of hereditary tubo-ovarian cancer susceptibility. These genes are considered

moderate-penetrance ovarian cancer predisposition genes, meaning that the magnitude and timing of risk generally differ from those observed in classic high-penetrance *BRCA1* disease. The American College of Medical Genetics and Genomics has emphasized that risk associated with these genes should be interpreted together with family history and other modifiers, supporting a personalized approach to preventive management rather than uniform intervention for all carriers (Ngeow et al., 2025).

Other hereditary syndromes broaden the spectrum further. Pathogenic *PTEN* variants characterize PTEN hamartoma tumor syndrome, including Cowden syndrome, which is associated with increased endometrial and breast cancer susceptibility. *STK11* pathogenic variants cause Peutz–Jeghers syndrome and may predispose to several gastrointestinal and gynecologic tumors, including sex cord tumors with annular tubules and adenoma malignum-type cervical neoplasia. *DICER1* tumor predisposition is associated with a distinctive spectrum that includes ovarian sex cord-stromal tumors, particularly Sertoli–Leydig cell tumors. These less frequent disorders demonstrate that hereditary gynecologic oncology encompasses multiple pathways of carcinogenesis rather than a single BRCA-centered model.

Lynch Syndrome and Hereditary Endometrial Cancer

Lynch syndrome represents the principal hereditary syndrome associated with endometrial cancer and is caused by pathogenic germline alterations affecting DNA mismatch repair, particularly *MLH1*, *MSH2*, *MSH6*, and *PMS2*, as well as deletions involving *EPCAM* that can lead to epigenetic inactivation of *MSH2*. Impaired mismatch repair results in the accumulation of replication errors, producing microsatellite instability and facilitating carcinogenesis.

An important feature of Lynch syndrome is its gene-specific penetrance. Data from the Prospective Lynch Syndrome Database have demonstrated that *MLH1* and *MSH2* pathogenic variants are associated with substantial risks of colorectal, endometrial, and ovarian malignancies, whereas *MSH6* is especially associated with increased endometrial cancer risk. In contrast, markedly lower risks have generally been observed with *PMS2*, illustrating why management strategies should not assume identical cancer susceptibility for all mismatch repair genes (Dominguez-Valentin et al., 2020).

Endometrial cancer may be the sentinel malignancy that leads to the diagnosis of Lynch syndrome in a previously unidentified family. Consequently, tumor-based screening has become increasingly relevant. Immunohistochemical evaluation of mismatch repair proteins and assessment of microsatellite instability can identify tumors with deficient mismatch repair and guide subsequent germline investigation. However, abnormal tumor testing does not automatically establish a hereditary diagnosis because mismatch repair deficiency can also result from somatic alterations, including *MLH1* promoter hypermethylation. Germline confirmation remains essential when a hereditary cause is suspected.

Clinical identification therefore requires integration of tumor phenotype, age at diagnosis, multiple primary malignancies, personal history, and family history. Exclusive dependence on traditional pedigree criteria may overlook individuals with pathogenic variants because family structures may be small, relatives may not have survived to cancer-prone ages, paternal inheritance may be underrecognized, or family medical information may be incomplete. The expansion of molecular screening addresses some of these limitations and allows hereditary risk assessment to be incorporated directly into oncologic care.

Clinical Identification and Genetic Testing

Identification of hereditary cancer susceptibility begins with systematic assessment of personal and family cancer history. Relevant characteristics include ovarian cancer at any age, early-onset malignancies, multiple primary tumors, clustering of breast, ovarian, pancreatic, prostate, colorectal, or endometrial cancers, rare tumor histologies, and previously identified pathogenic variants within the family. Nevertheless, modern recommendations increasingly extend genetic assessment beyond patients who fulfill highly restrictive family-history criteria.

For epithelial ovarian cancer, germline and somatic testing have become integral components of management. The Society of Gynecologic Oncology states that germline and somatic genetic testing can provide prognostic and therapeutic information and can also identify individuals whose relatives may benefit from cascade testing. Despite these benefits and professional recommendations supporting broad testing, only approximately one third of patients

were reported to complete germline or somatic genetic testing, illustrating a significant implementation gap (Gressel et al., 2024).

Multigene panel testing has further transformed hereditary cancer evaluation. Instead of sequentially analyzing individual genes based solely on clinical phenotype, next-generation sequencing allows simultaneous evaluation of multiple susceptibility genes. This approach can increase diagnostic yield, particularly in families whose cancer pattern overlaps several hereditary syndromes. However, increasing the number of analyzed genes also increases the likelihood of identifying variants of uncertain significance. Such variants should not be interpreted as disease-causing mutations and should not independently determine irreversible preventive interventions.

The selection of an appropriate gene panel therefore requires clinical context. NICE recommends choosing panels according to the individual's personal and family cancer history and supports referral for genetic counseling and testing in individuals with defined familial risk, known familial pathogenic variants, ovarian cancer, or relevant population-associated risk (NICE, 2024). The same guidance recognizes cascade testing as an important mechanism for identifying unaffected relatives who carry an established familial pathogenic variant.

Risk assessment should also incorporate more than the presence or absence of a pathogenic variant. Age, cancer history within the family, the specific gene involved, parity, hormonal exposure, and other modifying factors can alter estimated absolute risk. Current guidance consequently recommends the use of validated risk models where appropriate and emphasizes communication of personalized risk rather than relying exclusively on categorical genetic results (NICE, 2024).

Genetic Counseling and Family-Based Prevention

Genetic counseling constitutes a fundamental component of hereditary gynecologic cancer care. Before testing, patients should understand the potential outcomes of genetic analysis, including detection of a pathogenic or likely pathogenic variant, a negative result, or a variant of uncertain significance. Counseling should also address the limitations of testing, possible implications for relatives, reproductive considerations, psychological consequences, confidentiality, and the potential impact of results on surveillance and preventive interventions.

After a pathogenic germline variant is identified, counseling shifts toward interpretation of gene-specific risk and formulation of an individualized management strategy. The information obtained may also have important implications for first- and second-degree relatives. Cascade testing allows relatives to be tested specifically for the pathogenic variant already identified in the family, rather than undergoing broad testing without a defined target. Relatives who test negative for the familial alteration may avoid unnecessary hereditary-specific interventions, whereas carriers can enter surveillance or prevention programs before the development of malignancy.

This family-centered approach represents one of the principal preventive benefits of genetic oncology. A molecular diagnosis in one individual may therefore alter healthcare decisions across multiple generations. NICE specifically recommends genetic counseling and testing for first-degree relatives of individuals with a known pathogenic variant and provides pathways for more distant relatives when testing of intervening family members is not feasible (NICE, 2024).

Genetic counseling must nevertheless preserve informed and shared decision-making. The identification of elevated cancer risk can generate anxiety and difficult choices regarding fertility, preventive surgery, menopause, reproductive timing, and disclosure of genetic findings to relatives. Consequently, counseling should not be reduced to explaining laboratory results; it should help individuals interpret probabilistic information and make decisions compatible with their clinical circumstances and personal priorities.

Risk-Reduction Strategies

Management of hereditary gynecologic cancer susceptibility may incorporate surveillance, pharmacologic prevention in selected contexts, reproductive planning, and risk-reducing surgery. The choice depends primarily on the gene involved, magnitude of risk, age, previous malignancies, reproductive goals, and balance between expected benefit and potential adverse effects.

For women with high-risk *BRCA1* or *BRCA2* pathogenic variants, risk-reducing bilateral salpingo-oophorectomy represents the principal established strategy for reducing tubo-ovarian cancer risk once childbearing has been completed and the appropriate gene-specific age threshold has been reached. Observational evidence has shown substantial reductions in ovarian cancer incidence and mortality among *BRCA1/2* carriers undergoing risk-reducing surgery. In a large prospective analysis, salpingo-oophorectomy was associated with lower ovarian cancer risk and lower all-cause and ovarian cancer-specific mortality compared with women who had not undergone the procedure (Domchek et al., 2010).

However, risk-reducing salpingo-oophorectomy is not free of long-term consequences. When performed before natural menopause, abrupt estrogen deprivation may influence vasomotor symptoms, sexual function, bone health, cardiovascular health, and overall quality of life. These consequences emphasize the importance of timing surgery according to the natural history of each susceptibility gene rather than adopting a single age threshold for all hereditary syndromes.

This consideration is particularly important for *RAD51C*, *RAD51D*, and *BRIP1*. Contemporary ACMG recommendations recognize these as moderate-penetrance tubo-ovarian cancer genes and suggest consideration of risk-reducing salpingo-oophorectomy near the age of natural menopause, guided by age-specific risk, family history, and shared decision-making (Ngeow et al., 2025). This illustrates the transition from syndrome-based preventive medicine toward gene-specific risk management.

For Lynch syndrome, gynecologic risk reduction may include hysterectomy and bilateral salpingo-oophorectomy after completion of childbearing in appropriately selected carriers. The magnitude of expected benefit depends on the mismatch repair gene involved, particularly because endometrial and ovarian risks are not equivalent across *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Decisions should consequently integrate genotype, age, reproductive plans, comorbidities, and the individual's perception of risk.

Ovarian cancer surveillance remains a difficult area. Unlike several other malignancies, an effective screening strategy capable of reliably identifying early-stage ovarian cancer and reducing mortality in hereditary high-risk populations has not been firmly established. This limitation increases the importance of accurate genetic identification and appropriately timed preventive interventions. NICE therefore focuses management on individualized risk assessment, genetic counseling, risk-reducing surgery when indicated, and informed discussion of the limitations of surveillance rather than presenting screening as an equivalent substitute for proven preventive surgery (NICE, 2024).

Integration of Genetics, Oncology, and Gynecology

The management of hereditary gynecologic cancer ultimately requires coordination among clinical genetics, gynecology, gynecologic oncology, pathology, molecular diagnostics, primary care, and reproductive medicine. Genetic information has limited clinical value if pathogenic variants are identified without an established pathway for counseling, family testing, prevention, and long-term follow-up. Contemporary guidelines consequently emphasize referral systems connecting genetics services with multidisciplinary gynecologic oncology care (NICE, 2024).

The principal challenge is therefore no longer restricted to discovering hereditary cancer genes. It is increasingly centered on translating molecular information into proportionate and individualized clinical actions. High-penetrance genes, moderate-penetrance genes, and mismatch repair disorders require different interpretations of cancer probability, age of onset, organ-specific risk, and potential benefit from preventive intervention. The same molecular result may also have different implications depending on a patient's age, personal cancer history, reproductive goals, and familial context.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To **analyze and integrate** current clinical, oncologic, and genetic evidence on hereditary gynecologic cancer syndromes in order to identify individuals at increased inherited risk, evaluate the role of genetic counseling and

molecular testing, and determine appropriate risk-reduction strategies according to the specific hereditary syndrome, pathogenic variant, individual risk profile, reproductive considerations, and available evidence.

Specific Objectives

Cognitive Domain

1. To **identify** the principal hereditary syndromes associated with gynecologic malignancies, including hereditary breast and ovarian cancer syndrome, Lynch syndrome, PTEN hamartoma tumor syndrome, Peutz–Jeghers syndrome, and DICER1-related tumor predisposition.
2. To **describe** the molecular mechanisms and genes involved in hereditary gynecologic cancer susceptibility, with particular emphasis on *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BRIPI*, *RAD51C*, *RAD51D*, *PTEN*, *STK11*, and *DICER1*.
3. To **differentiate** high-penetrance and moderate-penetrance pathogenic variants according to their estimated association with ovarian, endometrial, breast, and other related malignancies.
4. To **analyze** the clinical and familial characteristics that should raise suspicion of hereditary cancer predisposition, including early age at diagnosis, multiple primary tumors, characteristic combinations of malignancies, unusual histologic subtypes, and clustering of cancer within a family.
5. To **compare** the indications, advantages, limitations, and clinical implications of germline testing, tumor molecular testing, multigene panels, mismatch repair immunohistochemistry, and microsatellite instability analysis.
6. To **evaluate** the clinical relevance of gene-specific penetrance and age-dependent cancer risk when establishing individualized surveillance and preventive strategies.
7. To **analyze** the role of pretest and post-test genetic counseling in the interpretation of pathogenic variants, negative results, and variants of uncertain significance.
8. To **evaluate** current risk-reduction strategies, including surveillance, cascade testing, reproductive counseling, risk-reducing salpingo-oophorectomy, hysterectomy, and other preventive interventions according to the hereditary syndrome involved.
9. To **integrate** evidence from gynecology, oncology, genetics, pathology, and preventive medicine to construct an individualized model for hereditary cancer risk assessment and management.

Psychomotor Domain

10. To **apply** a structured clinical assessment process for the collection and organization of personal and family cancer history in individuals with suspected hereditary gynecologic cancer predisposition.
11. To **construct** a multigenerational pedigree capable of identifying patterns compatible with autosomal dominant hereditary cancer transmission and potentially affected family members.
12. To **classify** patients according to their clinical and molecular characteristics in order to determine whether referral for specialized genetic evaluation is indicated.
13. To **interpret** genetic and molecular findings within the context of clinical information, distinguishing pathogenic or likely pathogenic variants from variants of uncertain significance and non-pathogenic findings.
14. To **develop** an individualized clinical decision pathway linking hereditary risk identification with genetic counseling, molecular testing, cascade testing, surveillance, and preventive interventions.
15. To **organize** gene-specific information regarding cancer risk, recommended surveillance, preventive surgery, and timing of intervention in a reproducible framework applicable to clinical decision-making.

Affective Domain

16. To **recognize** the psychological, reproductive, familial, and social implications associated with hereditary cancer risk and genetic testing.
17. To **value** informed consent, patient autonomy, confidentiality, and shared decision-making as fundamental components of hereditary cancer counseling.
18. To **promote** communication of hereditary risk in a clear, evidence-based, and non-directive manner, respecting individual preferences and reproductive goals.
19. To **appraise** the importance of multidisciplinary collaboration among gynecology, oncology, genetics, pathology, reproductive medicine, and primary care in the management of hereditary cancer syndromes.
20. To **support** a preventive clinical approach that considers not only cancer incidence reduction but also fertility, surgical menopause, quality of life, psychosocial impact, and long-term health.

OBJETO DE ESTUDIO

Object of Study

The object of study is the **clinical, genetic, and preventive management of hereditary gynecologic cancer syndromes**, with particular emphasis on the identification of individuals at increased inherited risk, the interpretation of germline and tumor molecular findings, the role of genetic counseling, and the selection of individualized strategies for cancer risk reduction.

The phenomenon under investigation comprises the interaction between **hereditary susceptibility, molecular alterations, clinical presentation, family history, and preventive decision-making** in individuals with confirmed or suspected predisposition to gynecologic malignancies. Particular attention is directed toward hereditary syndromes associated with ovarian, fallopian tube, endometrial, breast, and selected rare gynecologic tumors.

The principal hereditary conditions considered include **hereditary breast and ovarian cancer syndrome**, predominantly associated with pathogenic variants in *BRCA1* and *BRCA2*; **Lynch syndrome**, related to pathogenic alterations in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*; and other clinically relevant hereditary predisposition syndromes involving *BRIP1*, *RAD51C*, *RAD51D*, *PTEN*, *STK11*, and *DICER1*. These genes were selected because of their established or emerging association with increased susceptibility to gynecologic malignancies and their potential implications for clinical surveillance, family testing, reproductive counseling, and risk-reducing interventions.

The population of interest includes **adult women with a personal or family history suggestive of hereditary gynecologic cancer predisposition**, women diagnosed with ovarian, fallopian tube, primary peritoneal, or endometrial cancer who meet criteria for genetic evaluation, and unaffected individuals belonging to families in which a pathogenic germline variant has already been identified. The study also considers relatives who may benefit from cascade testing because hereditary cancer syndromes frequently affect several members of the same family across successive generations.

The study focuses specifically on several interrelated dimensions. The first is **clinical identification**, including age at cancer diagnosis, tumor type, histological characteristics, multiple primary malignancies, and patterns of cancer aggregation within families. The second is **molecular characterization**, including germline genetic testing, somatic tumor testing, multigene panels, mismatch repair protein immunohistochemistry, microsatellite instability analysis, and interpretation of pathogenic variants, likely pathogenic variants, and variants of uncertain significance.

A third dimension is **genetic counseling**, considered as the process through which patients and relatives receive information regarding inheritance patterns, cancer probability, implications of molecular findings, reproductive considerations, surveillance options, and the potential benefits and limitations of preventive interventions. Within this

framework, genetic counseling is analyzed not only as a diagnostic support tool but also as an essential mechanism for informed and shared decision-making.

The fourth dimension concerns **risk-reduction strategies**. These include gene-specific surveillance, risk-reducing bilateral salpingo-oophorectomy, hysterectomy in selected hereditary syndromes, cascade testing of relatives, reproductive planning, and other preventive measures applicable according to the individual's genetic and clinical profile. Special consideration is given to the timing of preventive surgery because the expected oncologic benefit must be balanced against fertility, surgical menopause, long-term endocrine effects, and quality of life.

Accordingly, the unit of analysis is not limited to the presence of a genetic mutation. Instead, it encompasses the **complete hereditary cancer risk pathway**, beginning with clinical suspicion and family history, continuing through molecular testing and genetic interpretation, and culminating in counseling, family-based risk assessment, surveillance, and preventive intervention.

The study therefore conceptualizes hereditary gynecologic cancer as a **multidimensional clinical-genetic phenomenon** in which molecular findings acquire practical relevance only when they are interpreted in conjunction with penetrance, age-specific cancer risk, personal and family history, reproductive goals, and patient preferences. This approach allows the investigation to examine how genetic information can be translated into individualized and clinically applicable preventive strategies.

In operational terms, the object of study can be summarized as the relationship between **hereditary genetic susceptibility and clinical decision-making in gynecologic oncology**, evaluating how the identification and interpretation of pathogenic variants can guide genetic counseling, cascade testing, surveillance, and interventions intended to reduce the incidence and consequences of hereditary gynecologic malignancies.

METODOLOGÍA

Methodological Approach

This study employed the **Scientific Method** through a structured integrative review of the available evidence concerning hereditary gynecologic cancer syndromes. This methodological approach was selected because the research question requires the integration of genetic, oncologic, gynecologic, preventive, and counseling-related evidence derived from different types of scientific publications, including clinical guidelines, consensus statements, prospective cohort studies, observational studies, systematic reviews, and relevant original investigations.

The methodology was designed to examine the relationship between hereditary genetic susceptibility and clinical decision-making, particularly the processes of identifying individuals at increased cancer risk, selecting appropriate molecular tests, interpreting genetic findings, providing genetic counseling, and implementing individualized risk-reduction strategies.

The Scientific Method was operationalized through the sequential stages of **problem definition, formulation of the research question and hypothesis, systematic identification of evidence, selection and classification of relevant information, comparative analysis, interpretation of findings, and synthesis of clinically applicable conclusions**.

Study Design

A **descriptive, analytical, and integrative literature review** was conducted. The study did not focus exclusively on the frequency of hereditary variants but evaluated the complete clinical pathway from suspicion of hereditary cancer predisposition to preventive management.

The analysis included evidence concerning:

- hereditary breast and ovarian cancer syndrome;
- Lynch syndrome;

- moderate-penetrance ovarian cancer susceptibility genes;
- PTEN hamartoma tumor syndrome;
- Peutz–Jeghers syndrome;
- DICER1-related tumor predisposition;
- genetic counseling;
- germline and somatic molecular testing;
- cascade testing;
- surveillance strategies;
- and risk-reducing surgical interventions.

The study was structured around three principal analytical domains: **clinical identification, genetic assessment and counseling, and cancer risk reduction.**

Sources of Information

The literature search was designed to identify scientific evidence indexed in major biomedical databases and authoritative clinical guidance repositories. The principal sources considered were:

PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, GeneReviews, National Comprehensive Cancer Network guidelines, National Institute for Health and Care Excellence guidelines, American Society of Clinical Oncology publications, Society of Gynecologic Oncology recommendations, and American College of Medical Genetics and Genomics clinical resources.

Additional references were identified through manual examination of the bibliographies of highly relevant articles and consensus documents in order to detect studies not captured during the initial search.

Search Strategy

The literature search combined controlled terminology and free-text terms related to hereditary cancer, gynecologic malignancy, molecular genetics, counseling, and prevention.

The principal search terms included:

“hereditary gynecologic cancer,” “hereditary ovarian cancer,” “hereditary endometrial cancer,” “BRCA1,” “BRCA2,” “Lynch syndrome,” “MLH1,” “MSH2,” “MSH6,” “PMS2,” “EPCAM,” “BRIP1,” “RAD51C,” “RAD51D,” “PTEN,” “STK11,” “DICER1,” “germline testing,” “somatic testing,” “multigene panel,” “genetic counseling,” “cascade testing,” “risk-reducing salpingo-oophorectomy,” “risk-reducing hysterectomy,” “ovarian cancer prevention,” and “hereditary cancer risk assessment.”

Boolean operators were used to combine concepts. A reproducible general search structure was established as follows:

(hereditary OR inherited OR germline) AND (gynecologic OR ovarian OR endometrial OR fallopian tube) AND (cancer OR malignancy) AND (genetic testing OR genetic counseling OR risk assessment OR prevention OR risk-reducing surgery).

Gene-specific searches were subsequently performed by replacing the hereditary predisposition component with the corresponding gene or syndrome.

Eligibility Criteria

Studies and clinical documents were selected according to predefined inclusion and exclusion criteria.

Inclusion Criteria

Publications were considered eligible when they:

1. Examined hereditary predisposition to ovarian, fallopian tube, peritoneal, endometrial, or other clinically relevant gynecologic malignancies.
2. Evaluated pathogenic or likely pathogenic germline variants associated with hereditary cancer susceptibility.
3. Addressed hereditary breast and ovarian cancer syndrome, Lynch syndrome, or other established gynecologic cancer predisposition syndromes.
4. Evaluated genetic testing, multigene panels, tumor molecular testing, mismatch repair assessment, microsatellite instability, or variant interpretation.
5. Examined genetic counseling, cascade testing, or family-based risk assessment.
6. Evaluated cancer surveillance or risk-reducing interventions, particularly salpingo-oophorectomy and hysterectomy.
7. Were published as clinical guidelines, consensus statements, systematic reviews, prospective or retrospective cohort studies, case-control studies, or other relevant clinical investigations.
8. Were available in English or Spanish.

Priority was assigned to contemporary evidence, while older landmark studies were retained when they provided fundamental information regarding cancer penetrance, hereditary syndromes, or the effectiveness of preventive surgery.

Exclusion Criteria

Publications were excluded when they:

1. Focused exclusively on sporadic gynecologic cancer without assessment of hereditary predisposition.
2. Examined molecular alterations restricted to tumor biology without implications for hereditary risk or clinical management.
3. Presented isolated case reports without broader relevance to risk assessment or clinical decision-making.
4. Provided insufficient methodological information.
5. Were duplicated across databases.
6. Focused exclusively on experimental laboratory models without direct clinical applicability.
7. Addressed hereditary syndromes without a relevant association with gynecologic malignancies.

Study Selection

The selection process was performed in sequential stages. First, titles were reviewed to eliminate publications clearly unrelated to hereditary gynecologic oncology. Second, abstracts were examined to determine their relevance to the predefined clinical and genetic domains. Third, potentially eligible publications underwent full-text assessment.

Documents were retained when they contributed information to at least one of the principal analytical categories:

hereditary syndrome identification, gene-specific cancer risk, clinical criteria for genetic assessment, molecular diagnosis, genetic counseling, cascade testing, surveillance, or risk-reducing intervention.

When several publications addressed the same clinical question, preference was given to recent clinical guidelines, systematic evidence syntheses, large prospective cohorts, and studies providing gene-specific risk estimates.

Data Extraction

Relevant information from each selected source was extracted using a standardized analytical framework. The following variables were considered:

- hereditary syndrome or gene evaluated;
- associated gynecologic malignancies;
- estimated cancer risk or penetrance;
- age-related patterns of risk;
- clinical criteria suggesting hereditary predisposition;
- type of molecular testing;
- interpretation of genetic findings;
- implications of pathogenic variants;
- recommendations for genetic counseling;
- indications for cascade testing;
- surveillance strategies;
- type and timing of risk-reducing surgery;
- reproductive implications;
- quality-of-life considerations;
- and major limitations of the available evidence.

This structure permitted comparison among hereditary syndromes with substantially different levels of penetrance and different clinical consequences.

Classification of Genetic Findings

Genetic information was interpreted according to its clinical relevance. Particular attention was given to **pathogenic and likely pathogenic variants**, as these findings may justify specific hereditary cancer management strategies.

Variants of uncertain significance were analyzed separately and were not considered equivalent to pathogenic variants. The study therefore distinguished between findings with established clinical implications and molecular alterations whose significance remains uncertain.

The analysis also differentiated **germline variants**, which may indicate inherited susceptibility and have implications for relatives, from **somatic alterations**, which may influence tumor classification or therapeutic decisions without necessarily establishing a hereditary syndrome.

Analytical Strategy

The selected evidence was analyzed using a comparative qualitative framework. The analysis was organized according to five principal dimensions:

1. **Molecular basis of hereditary susceptibility.**

2. **Clinical identification of high-risk individuals.**
3. **Genetic and molecular diagnostic strategies.**
4. **Genetic counseling and cascade testing.**
5. **Cancer risk-reduction strategies.**

For each dimension, findings were compared across hereditary syndromes and specific susceptibility genes.

Special emphasis was placed on differences between high-penetrance genes such as *BRCA1* and *BRCA2*, mismatch repair genes associated with Lynch syndrome, and moderate-penetrance ovarian cancer genes such as *BRIP1*, *RAD51C*, and *RAD51D*.

Rather than assuming uniform risk among all pathogenic variants, evidence was analyzed according to **gene-specific penetrance, age-dependent risk, tumor spectrum, reproductive considerations, and potential benefit of preventive intervention.**

Assessment of Evidence

The strength of evidence was evaluated according to the methodological characteristics of each source. Clinical practice guidelines and international consensus recommendations were used primarily to determine current management strategies, while large cohort studies and prospective registries were used to analyze cancer penetrance and age-specific risk.

Observational investigations were considered when randomized clinical trials were unavailable or ethically impractical, particularly for prophylactic surgery and hereditary cancer prevention.

When recommendations differed among sources, the analysis considered differences in study population, gene penetrance, age-specific risk, follow-up duration, clinical setting, and publication date before integrating the findings.

Variables of Interest

The primary variables analyzed were:

Independent variables: hereditary syndrome, affected gene, pathogenic variant status, family cancer history, age, and previous cancer diagnosis.

Intermediate clinical variables: estimated penetrance, age-specific cancer risk, molecular test results, and eligibility for genetic counseling or cascade testing.

Outcome-related variables: recommendation for surveillance, indication and timing of preventive surgery, family testing, reproductive counseling, and anticipated reduction in hereditary cancer risk.

This organization allowed the analysis to evaluate how molecular and clinical characteristics influence preventive decision-making.

Ethical Considerations

Because the study was based on previously published scientific evidence and did not involve direct intervention with human participants, no identifiable patient information was collected.

Nevertheless, ethical principles relevant to genetic medicine were incorporated into the analytical framework, particularly **autonomy, confidentiality, informed consent, nondirective genetic counseling, communication of hereditary information, reproductive decision-making, and respect for individual preferences.**

Special consideration was given to the fact that germline genetic findings may have implications not only for the individual tested but also for biologically related family members.

Reproducibility

To facilitate reproducibility, the methodology establishes explicit databases, search concepts, eligibility criteria, analytical categories, data extraction variables, and evidence classification procedures. Another investigator applying the same search structure and inclusion criteria should be able to identify a comparable body of literature and reproduce the principal analytical steps.

The methodological design therefore provides a structured pathway from the identification of the research problem to the synthesis of clinically applicable evidence, allowing hereditary gynecologic cancer syndromes to be evaluated through an integrated framework involving genetics, oncology, gynecology, counseling, and cancer prevention.

FASES DEL DESARROLLO

Phase 1. Identification and Definition of the Research Problem

The first phase consisted of defining the central problem of the study: the difficulty of integrating hereditary risk identification, molecular diagnosis, genetic counseling, and preventive decision-making within a unified framework for gynecologic oncology.

The problem was approached from the recognition that hereditary gynecologic cancers are genetically heterogeneous and that different pathogenic variants confer distinct levels of penetrance, age-specific risk, tumor spectrum, and preventive implications. Therefore, the study did not assume that all hereditary cancer syndromes should be managed through identical strategies.

During this phase, the principal clinical challenge was defined as the need to determine how molecular and familial information can be translated into individualized preventive actions.

Phase 2. Formulation of the Research Question and Hypothesis

Once the problem had been defined, the research question was established:

How can clinical identification, genetic evaluation, and individualized risk-reduction strategies be integrated to optimize the management of individuals with hereditary predisposition to gynecologic cancer?

The working hypothesis proposed that an integrated clinical-genetic approach based on personal and family history, molecular findings, gene-specific penetrance, genetic counseling, and individualized prevention provides a more comprehensive model for hereditary cancer management than approaches based exclusively on family history or isolated genetic findings.

This phase guided the selection of search terms, eligibility criteria, analytical variables, and the organization of the subsequent evidence synthesis.

Phase 3. Definition of the Analytical Framework

The third phase established the conceptual structure used throughout the review.

Five principal analytical domains were defined:

1. hereditary genetic susceptibility;
2. clinical identification of high-risk individuals;
3. molecular and genetic testing;
4. genetic counseling and cascade testing;
5. risk-reduction strategies.

Each selected publication was evaluated according to one or more of these domains.

This structure allowed the study to maintain consistency when comparing syndromes with different molecular mechanisms, such as hereditary breast and ovarian cancer syndrome, Lynch syndrome, PTEN hamartoma tumor syndrome, Peutz–Jeghers syndrome, and DICER1-related tumor predisposition.

Phase 4. Literature Search and Evidence Identification

A structured search of scientific and clinical literature was then conducted using combinations of hereditary cancer, gynecologic oncology, molecular genetics, genetic counseling, and prevention-related terms.

Searches were performed using the predefined keywords and Boolean combinations described in the methodology section.

Priority was given to literature addressing:

- *BRCA1* and *BRCA2*;
- mismatch repair genes associated with Lynch syndrome;
- *BRIP1*, *RAD51C*, and *RAD51D*;
- *PTEN*, *STK11*, and *DICER1*;
- germline and somatic testing;
- multigene panels;
- cascade testing;
- surveillance;
- and risk-reducing surgery.

The search strategy was broadened when necessary through manual examination of reference lists from highly relevant articles and clinical guidelines.

Phase 5. Screening and Selection of Evidence

All potentially relevant publications were assessed according to the predefined inclusion and exclusion criteria.

The screening process was conducted in three sequential steps:

First, titles were reviewed to eliminate clearly unrelated publications.

Second, abstracts were evaluated to determine whether the study addressed hereditary susceptibility, gynecologic malignancy, genetic evaluation, counseling, or prevention.

Third, full-text assessment was performed for publications considered potentially eligible.

Documents were excluded when they focused exclusively on sporadic cancer, lacked clinical relevance to hereditary gynecologic oncology, presented insufficient methodological information, or duplicated previously identified evidence.

Phase 6. Extraction and Organization of Information

The selected sources were then analyzed using a standardized extraction framework.

For each publication, the following information was recorded:

- hereditary syndrome;

- susceptibility gene;
- gynecologic malignancies associated with the syndrome;
- estimated cancer risk;
- age-specific penetrance;
- clinical characteristics suggesting hereditary predisposition;
- diagnostic tests used;
- interpretation of molecular findings;
- recommendations for genetic counseling;
- cascade testing strategies;
- surveillance recommendations;
- risk-reducing interventions;
- timing of preventive surgery;
- reproductive implications;
- and relevant limitations.

The extracted information was organized by hereditary syndrome and clinical domain to allow direct comparison between different genetic conditions.

Phase 7. Classification of Hereditary Risk

In this phase, the evidence was classified according to the magnitude and clinical relevance of hereditary cancer susceptibility.

Genes and syndromes were grouped according to characteristics such as:

- high or moderate penetrance;
- principal malignancies involved;
- age-related risk;
- quality of available evidence;
- and existence of established preventive recommendations.

Particular attention was given to distinguishing high-penetrance syndromes from moderate-risk susceptibility genes, because the expected benefit and timing of preventive interventions may differ substantially.

Genetic findings were also categorized as pathogenic or likely pathogenic variants, variants of uncertain significance, or findings without established clinical relevance.

Phase 8. Comparative Analysis of Clinical Identification Strategies

The next phase evaluated how hereditary cancer susceptibility can be identified in clinical practice.

The analysis included:

- personal cancer history;

- family cancer history;
- age at diagnosis;
- bilateral or multiple primary tumors;
- characteristic tumor combinations;
- rare histological findings;
- presence of previously identified familial pathogenic variants;
- mismatch repair deficiency;
- microsatellite instability;
- and molecular findings obtained through multigene panels.

The objective of this phase was to determine which combinations of clinical and molecular findings most consistently support referral for hereditary cancer evaluation.

Phase 9. Analysis of Genetic Testing and Variant Interpretation

During this phase, germline and somatic testing approaches were compared.

The analysis evaluated the role of:

- germline sequencing;
- tumor molecular testing;
- multigene hereditary cancer panels;
- mismatch repair immunohistochemistry;
- microsatellite instability analysis;
- and complementary molecular investigations.

Special attention was given to the distinction between germline and somatic alterations because their implications differ substantially.

A germline pathogenic variant may indicate inherited susceptibility and justify cascade testing, whereas a somatic alteration may primarily influence tumor biology or therapeutic management.

Variants of uncertain significance were analyzed separately to prevent inappropriate interpretation as pathogenic findings.

Phase 10. Evaluation of Genetic Counseling and Cascade Testing

The tenth phase focused on the role of genetic counseling before and after molecular testing.

Pretest counseling was analyzed in relation to informed consent, possible test outcomes, reproductive implications, psychological effects, and the consequences of discovering hereditary susceptibility.

Post-test counseling was evaluated according to the interpretation of positive, negative, and uncertain results.

The study also examined cascade testing as a family-based prevention strategy, considering how identification of a pathogenic variant in one individual may permit targeted evaluation of relatives who have not yet developed cancer.

Phase 11. Evaluation of Risk-Reduction Strategies

Risk-reducing interventions were then analyzed according to hereditary syndrome and gene-specific cancer risk.

The principal strategies evaluated included:

- clinical surveillance;
- risk-reducing bilateral salpingo-oophorectomy;
- hysterectomy in selected Lynch syndrome carriers;
- individualized timing of preventive surgery;
- reproductive planning;
- family testing;
- and long-term follow-up.

Each intervention was considered according to the balance between potential cancer prevention and possible adverse consequences, including infertility, surgical menopause, endocrine effects, sexual health, bone health, and quality of life.

Phase 12. Comparative Integration of the Evidence

Once each domain had been analyzed separately, the findings were integrated into a comparative framework.

This phase examined how clinical and preventive decisions differ according to:

- the gene involved;
- penetrance;
- age-specific cancer risk;
- tumor spectrum;
- family history;
- previous cancer diagnosis;
- reproductive status;
- and patient preferences.

The goal was not to establish one universal management strategy but to identify the factors that justify individualized decision-making.

Phase 13. Construction of an Integrated Clinical Pathway

Based on the comparative evidence, an integrated clinical pathway was developed.

The proposed sequence was:

clinical suspicion → family history assessment → hereditary risk evaluation → selection of molecular testing → interpretation of genetic findings → genetic counseling → cascade testing → individualized surveillance or preventive intervention → long-term follow-up.

This pathway was designed to connect genetic information directly with clinical action and to facilitate multidisciplinary coordination.

Phase 14. Interpretation of Findings

The integrated evidence was subsequently interpreted in relation to the original research question and hypothesis.

The analysis focused on whether the available evidence supports the use of gene-specific and individualized hereditary cancer management rather than uniform recommendations for all pathogenic variants.

The interpretation also considered areas in which evidence remains incomplete, particularly moderate-penetrance genes, long-term outcomes of emerging preventive strategies, and disparities in access to genetic services.

RESULTADOS Y DISCUSIÓN

Figure 1.

Cumulative ovarian cancer risk in BRCA1 and BRCA2 pathogenic variant carriers

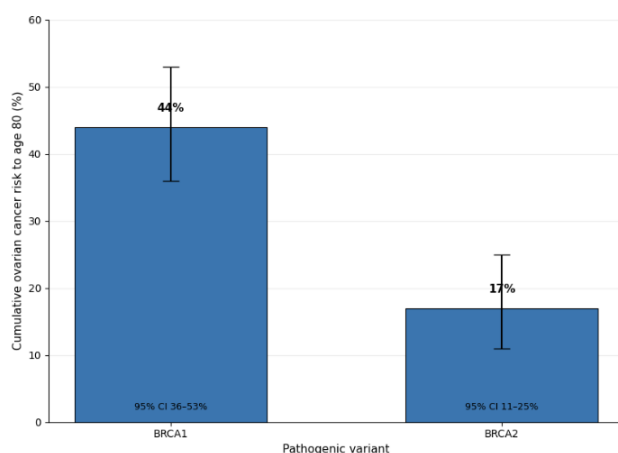


Figure 1 demonstrates a marked difference in the cumulative risk of ovarian cancer between carriers of pathogenic variants in *BRCA1* and *BRCA2*. By 80 years of age, the estimated cumulative ovarian cancer risk reached **44% among BRCA1 carriers**, with a 95% confidence interval (CI) of **36%–53%**, compared with **17% among BRCA2 carriers**, with a 95% CI of **11%–25%**. These estimates were obtained from a large prospective cohort study evaluating cancer incidence among carriers of pathogenic *BRCA1* and *BRCA2* variants (Kuchenbaecker et al., 2017).

In absolute terms, the difference between the two groups was **27 percentage points**, with the cumulative estimate for *BRCA1* being approximately **2.6 times** that observed for *BRCA2*. Therefore, although both genes were associated with a considerable cumulative probability of ovarian cancer, the magnitude of the observed risk was substantially greater among *BRCA1* carriers. The 95% confidence intervals also remained clearly separated: the upper estimate for *BRCA2* reached 25%, while the lower limit for *BRCA1* was 36%. This pattern shows that the difference was not restricted to the central estimates but remained evident across the reported uncertainty ranges (Kuchenbaecker et al., 2017).

The prospective study from which these data were obtained included **9,856 women carrying pathogenic variants in either BRCA1 or BRCA2** across the different cancer analyses. Specifically, **5,066 women were eligible for the ovarian cancer analysis**, with a median age of 38 years at entry. During follow-up, 109 incident ovarian cancers were documented. The cumulative risk estimates were calculated using prospective follow-up data, with women censored at the time of risk-reducing salpingo-oophorectomy in the ovarian cancer analysis, thereby reducing distortion of the natural risk estimates caused by preventive removal of the ovaries and fallopian tubes (Kuchenbaecker et al., 2017).

The age-related incidence pattern also differed quantitatively between the two hereditary groups. Ovarian cancer incidence increased with age in carriers of both genes, reaching higher levels during later adulthood, but incidence was consistently greater among *BRCA1* carriers. In the original prospective analysis, the comparison of ovarian cancer incidence between *BRCA1* and *BRCA2* yielded a **hazard ratio of 3.6 (95% CI, 2.2–5.9; $p < .001$)**, indicating a

statistically significant difference in the rate of ovarian cancer occurrence between the two genetic groups during follow-up (Kuchenbaecker et al., 2017).

The graph consequently reveals two quantitatively distinct hereditary risk profiles. For every 100 women carrying a pathogenic *BRCA1* variant, the cumulative estimate suggests that approximately **44 could develop ovarian cancer by age 80**, whereas the corresponding estimate among 100 *BRCA2* carriers is approximately 17. These values are population-level cumulative estimates and should not be interpreted as deterministic outcomes for an individual carrier. Nevertheless, they provide a direct numerical representation of the different penetrance observed between these two major hereditary ovarian cancer susceptibility genes.

Another relevant finding is the width of the confidence intervals surrounding the cumulative estimates. For *BRCA1*, the estimated interval extends from 36% to 53%, while for *BRCA2* it ranges from 11% to 25%. Despite this statistical uncertainty, the estimates maintain a clear separation between the two genes. The central estimate for *BRCA1* exceeds the upper confidence boundary reported for *BRCA2* by **19 percentage points**, reinforcing the descriptive distinction between the two hereditary risk distributions.

These results also demonstrate why reporting hereditary ovarian cancer simply as “BRCA-associated” can conceal substantial differences within the category. Although *BRCA1* and *BRCA2* are both components of hereditary breast and ovarian cancer syndrome, the prospective data do not show equivalent ovarian cancer penetrance. Instead, the observed cumulative probabilities form distinct gene-specific patterns, with *BRCA1* displaying the higher ovarian cancer burden throughout the analyzed age range (Kuchenbaecker et al., 2017).

Figure 2.

Gene-specific gynecologic cancer risk in Lynch syndrome

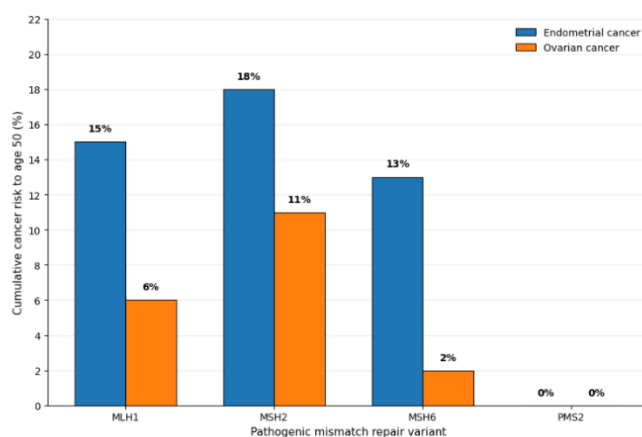


Figure 2 shows substantial gene-specific heterogeneity in gynecologic cancer risk among women carrying pathogenic mismatch repair variants associated with Lynch syndrome. By 50 years of age, the reported cumulative risks of endometrial cancer were **15% for MLH1, 18% for MSH2, 13% for MSH6, and 0% for PMS2**, whereas the corresponding cumulative risks of ovarian cancer were **6%, 11%, 2%, and 0%**, respectively. These prospective estimates demonstrate that the gynecologic cancer profile of Lynch syndrome differs considerably according to the affected mismatch repair gene rather than representing a uniform hereditary risk category (Dominguez-Valentin et al., 2021).

Among the four genes analyzed, *MSH2* displayed the highest cumulative risk for both malignancies before age 50. Endometrial cancer reached **18%**, while ovarian cancer reached **11%**. The absolute difference between the two cancer types within the *MSH2* group was therefore 7 percentage points. Furthermore, the ovarian cancer estimate observed

for *MSH2* was nearly twice that reported for *MLH1* and more than five times that reported for *MSH6*. This pattern identifies *MSH2* as the gene with the greatest observed combined gynecologic cancer burden in this age range within the analyzed dataset.

Carriers of pathogenic *MLH1* variants demonstrated the second-highest overall pattern. By age 50, cumulative endometrial cancer risk was **15%**, compared with **6%** for ovarian cancer. Endometrial risk was consequently 9 percentage points higher than ovarian risk. The prospective Lynch Syndrome Database has previously characterized *MLH1* and *MSH2* as highly penetrant Lynch syndrome genes with broadly similar patterns of colorectal, endometrial, and ovarian malignancy, although organ-specific and age-specific risks remain distinguishable between them (Dominguez-Valentin et al., 2020).

A different distribution was observed for *MSH6*. Its cumulative endometrial cancer risk reached **13% by age 50**, only moderately lower than the estimates observed for *MLH1* and *MSH2*. In contrast, ovarian cancer risk was only **2%** during the same period. The resulting 11-percentage-point difference between endometrial and ovarian cancer was the largest within-gene disparity among *MLH1*, *MSH2*, and *MSH6*. This numerical pattern is consistent with the broader prospective evidence showing that pathogenic *MSH6* variants exhibit a particularly prominent association with endometrial malignancy compared with several other Lynch-associated cancer manifestations (Dominguez-Valentin et al., 2020).

The *PMS2* group differed notably from the other three genes. No measurable cumulative endometrial or ovarian cancer risk before age 50 was demonstrated in the dataset represented in Figure 2. The larger prospective study of 6,350 carriers similarly reported that it did not demonstrate a statistically significant overall increase in cancer risk among pathogenic *PMS2* variant carriers during the analyzed prospective follow-up. However, these values should not be interpreted as proof that *PMS2* carriers have absolutely no lifetime gynecologic cancer risk; rather, they indicate the absence of a demonstrable premenopausal signal within the prospective observations used for these estimates (Dominguez-Valentin et al., 2020, 2021).

When the four genes are compared directly, endometrial cancer represents the numerically dominant gynecologic malignancy before age 50 for *MLH1*, *MSH2*, and *MSH6*. The difference between endometrial and ovarian cancer risk was **9 percentage points for MLH1**, **7 percentage points for MSH2**, and **11 percentage points for MSH6**. Consequently, the relative composition of gynecologic cancer risk varies not only in magnitude but also in the distribution between uterine and ovarian malignancies.

The ovarian cancer results demonstrate particularly marked heterogeneity. The reported cumulative risk ranged from **11% for MSH2** to **6% for MLH1**, **2% for MSH6**, and **0% for PMS2** before age 50. Thus, the difference between the highest and lowest measurable ovarian cancer estimates was 11 percentage points. The original analysis also reported prospectively observed ovarian cancer cases used in survival analyses across these genes, with substantially larger numbers for *MLH1* and *MSH2* than for *MSH6* or *PMS2*, indicating that estimates for the latter groups were based on fewer events and therefore require greater caution (Dominguez-Valentin et al., 2021).

The underlying prospective dataset strengthens the descriptive comparison. In the risk-reducing surgery analysis, the investigators reported **7,838 observed female-years for MLH1**, **5,487 for MSH2**, **1,614 for MSH6**, and **862 for PMS2** meeting the study selection criteria. These differences in observation time are important when describing the results because the precision of the gene-specific estimates is not identical across the four groups. The investigators specifically noted wider uncertainty for *MSH6* and *PMS2* estimates because of the smaller number of observed cases and carriers (Dominguez-Valentin et al., 2021).

The pattern shown in Figure 2 therefore separates Lynch syndrome into distinct gynecologic risk profiles. *MSH2* produced the highest observed cumulative risk for both endometrial and ovarian malignancy before age 50; *MLH1* showed substantial risks for both cancers; *MSH6* demonstrated a predominantly endometrial pattern; and *PMS2* showed no measurable premenopausal gynecologic cancer risk in these prospective estimates.

Figure 3.

Ovarian cancer risk associated with hereditary susceptibility genes

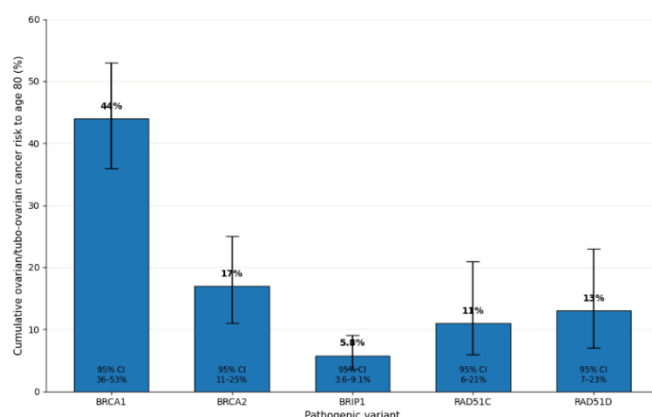


Figure 3 presents the cumulative risk of ovarian or tubo-ovarian cancer by 80 years of age among carriers of pathogenic variants in five hereditary susceptibility genes: *BRCA1*, *BRCA2*, *BRIP1*, *RAD51C*, and *RAD51D*. The estimates demonstrate a pronounced quantitative gradient across the genes analyzed. The highest cumulative risk was observed for *BRCA1*, at 44% (95% CI, 36%–53%), followed by *BRCA2* at 17% (95% CI, 11%–25%), *RAD51D* at 13% (95% CI, 7%–23%), *RAD51C* at 11% (95% CI, 6%–21%), and *BRIP1* at 5.8% (95% CI, 3.6%–9.1%).

The most prominent numerical finding was the separation of *BRCA1* from the remaining susceptibility genes. Its cumulative risk estimate of 44% was 27 percentage points higher than the estimate for *BRCA2*, 31 percentage points higher than *RAD51D*, 33 percentage points higher than *RAD51C*, and 38.2 percentage points higher than *BRIP1*. Expressed as a ratio of the central estimates, cumulative ovarian cancer risk associated with *BRCA1* was approximately 2.6 times that of *BRCA2*, 3.4 times that of *RAD51D*, 4 times that of *RAD51C*, and approximately 7.6 times that of *BRIP1*. The prospective *BRCA1/2* analysis reported a cumulative ovarian cancer risk to age 80 of 44% for *BRCA1* and 17% for *BRCA2*, demonstrating substantial heterogeneity even between the two principal genes associated with hereditary breast and ovarian cancer syndrome (Kuchenbaecker et al., 2017).

BRCA2 represented the second-highest central estimate in the comparison. Its cumulative risk of 17% exceeded the estimate for *RAD51D* by 4 percentage points, *RAD51C* by 6 percentage points, and *BRIP1* by 11.2 percentage points. However, the corresponding confidence interval of 11%–25% overlapped those reported for *RAD51C* and *RAD51D*. Therefore, while the central estimates can be ordered descriptively, the uncertainty ranges indicate that the precise magnitude of risk for these genes cannot be considered completely separated on the basis of point estimates alone.

Among the three additional homologous recombination genes, *RAD51D* demonstrated the highest cumulative estimate, reaching 13% by age 80, with a 95% confidence interval of 7%–23%. *RAD51C* followed at 11%, with a considerably broad 95% confidence interval of 6%–21%. The difference between the two central estimates was therefore only 2 percentage points. Yang et al. analyzed thousands of families and estimated cumulative tubo-ovarian cancer risks to age 80 of 11% for *RAD51C* and 13% for *RAD51D*. The study also reported strong associations with tubo-ovarian cancer, with relative risks of approximately 7.55 for *RAD51C* and 7.60 for *RAD51D* compared with population expectations.

The confidence intervals for *RAD51C* and *RAD51D* were substantially wider relative to their point estimates than those shown for *BRCA1*. For *RAD51C*, the interval extended from 6% to 21%, representing a 15-percentage-point span, whereas the *RAD51D* interval extended from 7% to 23%, a span of 16 percentage points. These intervals demonstrate the greater statistical uncertainty surrounding their absolute cumulative risk estimates.

Figure 4.

Completion of genetic testing among patients with ovarian cancer

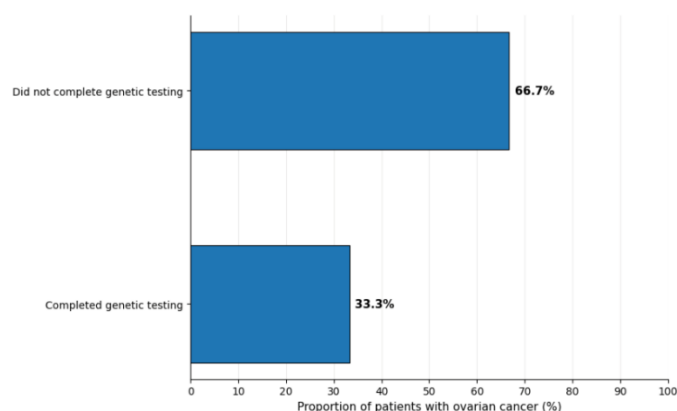


Figure 4 represents the proportion of patients with ovarian cancer reported to complete germline or somatic genetic testing in the evidence summarized by the Society of Gynecologic Oncology. Approximately **one third of patients (33.3%)** were represented as completing genetic testing, whereas approximately **two thirds (66.7%)** were represented as not completing testing. The 33.3% value is a graphical operationalization of the “about one third” estimate reported by Gressel et al. (2024), rather than a newly calculated pooled prevalence. Consequently, the complementary 66.7% represents the approximate proportion remaining outside completed genetic testing according to the same descriptive estimate (Gressel et al., 2024).

The numerical distribution shows a difference of approximately **33.4 percentage points** between patients represented as completing testing and those not completing it. Expressed comparatively, the group without completed testing was approximately twice the size of the group with completed testing. Therefore, for every 100 patients represented by the estimate, approximately 33 would have completed germline or somatic genetic testing, while approximately 67 would not have completed such testing.

This pattern was reported despite consensus recommendations supporting broad genetic evaluation in epithelial ovarian cancer. The Society of Gynecologic Oncology Clinical Practice Statement indicates that germline and somatic testing are established components of ovarian cancer care and notes that several professional organizations recommend universal genetic testing for this patient population. Nevertheless, the same statement reports that only about one third of patients complete germline or somatic genetic testing, demonstrating a substantial difference between the population considered eligible for testing and the proportion in whom testing is actually completed (Gressel et al., 2024).

The observed proportion should be interpreted as a broad summary of testing implementation rather than as a fixed rate applicable to every healthcare setting. Individual institutional studies have reported different completion rates. For example, a retrospective analysis of **367 women with ovarian cancer** found that **55.3% completed germline testing**, whereas **27.0% received somatic testing**. These two percentages represented different testing modalities and were not mutually exclusive, but they demonstrate that completion rates can vary depending on the type of genetic assessment examined and the clinical environment in which testing is delivered. The same investigation identified substantial differences between treatment settings, with germline testing performed in 60.4% of patients at a comprehensive cancer center compared with 38.1% at a safety-net hospital (Frey et al., 2019).

More recent institutional data have also demonstrated variation in genetic testing uptake. In a cohort of **459 ovarian cancer patients** treated at a comprehensive cancer center, **307 patients (67%) were referred for genetic counseling and 285 (62%) completed germline genetic testing**. The probability of completing testing differed substantially according to whether a genetic counseling referral had occurred: the predicted probability of completion was **0.83 (95% CI, 0.77–0.88)** among referred patients compared with **0.27 (95% CI, 0.18–0.35)** among those without referral. These findings show that testing rates reported in individual specialized centers may exceed the broader approximate one-third estimate summarized by the SGO statement (Miller et al., 2024).

Additional evidence evaluating electronic medical records among patients with epithelial ovarian cancer similarly reported genetic testing in **62% of patients** in a single institutional cohort. Among those tested, pathogenic variants

were identified in approximately **29%**, although documentation of complete laboratory reports was inconsistent. These data again demonstrate that completion estimates vary according to institution, period of observation, testing infrastructure, and how completion is defined (Bednar et al., 2023).

The variability across studies is therefore an important descriptive characteristic of the available evidence. While the SGO Clinical Practice Statement summarizes overall completion as approximately one third, individual cohorts have reported germline testing rates exceeding 50% and, in selected comprehensive cancer centers, approaching or exceeding 60%. The variation indicates that the proportion represented in Figure 4 should be understood as a broad estimate of implementation rather than an exact universal frequency.

The distinction between **germline** and **somatic** testing is also relevant when interpreting the reported percentages. Germline testing evaluates inherited pathogenic variants that may be present throughout the individual's cells and may therefore have implications for hereditary susceptibility and biologically related family members. Somatic testing evaluates alterations present within tumor tissue and may identify molecular characteristics relevant to the malignancy itself. Studies reporting completion of one modality cannot automatically be considered equivalent to studies measuring completion of both modalities. Gressel et al. (2024) explicitly addressed both germline and somatic testing in their clinical practice statement, which is why Figure 4 represents overall completion of either form according to their approximate summary estimate.

The data also show that genetic testing utilization cannot be described solely by a single percentage without considering the clinical pathway preceding test completion. Referral itself represents a measurable intermediate step. In the 459-patient cohort, 67% received a referral but 62% ultimately completed testing, producing a five-percentage-point difference between referral and completed molecular evaluation. Furthermore, patients who had received a referral demonstrated a substantially higher modeled probability of test completion than those without referral. These measurements illustrate that the testing process contains several sequential stages and that completion represents the final outcome of multiple preceding clinical actions.

Figure 4 therefore captures one of the principal implementation-related findings identified in the reviewed literature: the availability and recommendation of genetic testing do not correspond to universal completion. Using the SGO summary estimate, approximately **33.3%** of patients are represented as completing germline or somatic testing compared with approximately **66.7%** who do not. Individual studies demonstrate higher rates in some institutions, including germline completion rates of **55.3%**, **62%**, and **62%** in different cohorts, confirming considerable variability across healthcare environments (Gressel et al., 2024).

Figure 5.

Outcomes associated with risk-reducing surgery in hereditary cancer susceptibility

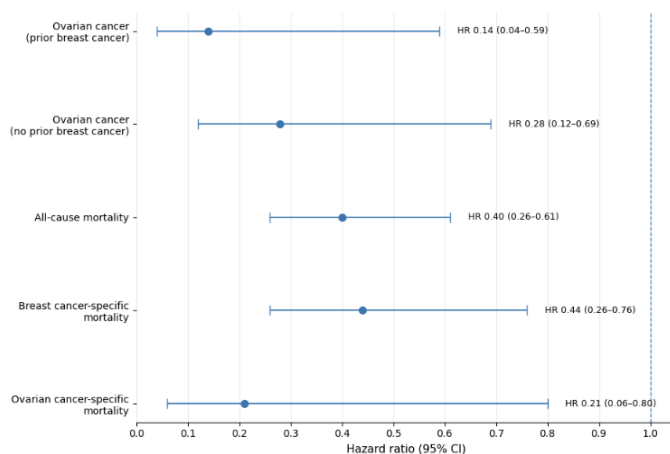


Figure 5 summarizes the hazard ratios reported for cancer-related outcomes and mortality among women carrying pathogenic *BRCA1* or *BRCA2* variants who underwent risk-reducing salpingo-oophorectomy compared with those who did not undergo the procedure. All five hazard ratio estimates were below 1.00, and all corresponding 95% confidence intervals remained below the null value of 1.00. The outcomes represented were ovarian cancer among women with a previous history of breast cancer, ovarian cancer among women without previous breast cancer, all-cause mortality, breast cancer-specific mortality, and ovarian cancer-specific mortality (Domchek et al., 2010).

The strongest association observed in the figure corresponded to ovarian cancer among women with a prior diagnosis of breast cancer. In this group, risk-reducing salpingo-oophorectomy was associated with a hazard ratio of **0.14 (95% CI, 0.04–0.59)**. Numerically, this HR corresponds to an approximately **86% lower relative hazard** compared with women who did not undergo the procedure. The original study also reported ovarian cancer occurrence of approximately **1% among women undergoing salpingo-oophorectomy compared with 6% among those who did not undergo surgery** in the subgroup with previous breast cancer (Domchek et al., 2010).

Among women without a previous diagnosis of breast cancer, the hazard ratio for ovarian cancer was **0.28 (95% CI, 0.12–0.69)**. This estimate corresponds numerically to an approximately **72% reduction in relative hazard**. In the reported cohort, ovarian cancer occurred in approximately **2% of women who underwent risk-reducing salpingo-oophorectomy compared with 6% of women who did not undergo the procedure**. Although the point estimate was higher than that observed in women with previous breast cancer, the confidence interval remained entirely below 1.00 (Domchek et al., 2010).

When mortality outcomes were analyzed, risk-reducing salpingo-oophorectomy was associated with an **all-cause mortality HR of 0.40 (95% CI, 0.26–0.61)**. This corresponds to an approximately **60% lower relative hazard of death from any cause** during the analyzed follow-up. The original cohort reported all-cause mortality of approximately **3% among women undergoing salpingo-oophorectomy versus 10% among women who did not undergo the procedure**. The confidence interval ranged from 0.26 to 0.61 and did not cross the reference value of 1.00 (Domchek et al., 2010).

Breast cancer-specific mortality demonstrated a hazard ratio of **0.44 (95% CI, 0.26–0.76)**. Expressed descriptively, this corresponds to an approximately **56% lower relative hazard of breast cancer-specific death** in the surgery group. Breast cancer-specific mortality was reported in approximately **2% of women who underwent risk-reducing salpingo-oophorectomy compared with 6% of those who did not**. Among the five outcomes represented in Figure 5, this was the highest point estimate, although it remained substantially below 1.00 (Domchek et al., 2010).

Ovarian cancer-specific mortality showed one of the lowest hazard ratios in the analysis, at **0.21 (95% CI, 0.06–0.80)**. This value corresponds numerically to an approximately **79% lower relative hazard of ovarian cancer-related death**. In the cohort, ovarian cancer-specific mortality was approximately **0.4% among women undergoing salpingo-oophorectomy compared with 3% among those who did not undergo surgery**. Although the confidence interval was wider than those observed for all-cause mortality and breast cancer-specific mortality, its upper boundary remained below 1.00 (Domchek et al., 2010).

The confidence intervals shown in Figure 5 also demonstrate differences in statistical precision among outcomes. The estimate for all-cause mortality had a relatively narrow interval of **0.26–0.61**, whereas the ovarian cancer-specific mortality estimate ranged from **0.06 to 0.80**. Similarly, the ovarian cancer HR among women with previous breast cancer ranged from **0.04 to 0.59**, reflecting greater uncertainty around a comparatively low point estimate. These differences are consistent with variation in the number of events recorded for each outcome.

When the five estimates are compared directly, the hazard ratios can be ordered descriptively from lowest to highest as follows: ovarian cancer among women with previous breast cancer (**0.14**), ovarian cancer-specific mortality (**0.21**), ovarian cancer among women without previous breast cancer (**0.28**), all-cause mortality (**0.40**), and breast cancer-specific mortality (**0.44**). Thus, the full range of observed hazard ratios extended from 0.14 to 0.44.

The study from which these results were derived included **2,482 women with pathogenic BRCA1 or BRCA2 variants** recruited through 22 clinical and research genetics centers in Europe and North America. Participants were followed prospectively through the end of 2009. The analysis evaluated breast and ovarian cancer occurrence, cancer-

specific mortality, and overall mortality in relation to risk-reducing mastectomy and salpingo-oophorectomy (Domchek et al., 2010).

Additional gene-stratified analyses reported that among *BRCA1* carriers without previous breast cancer, risk-reducing salpingo-oophorectomy was associated with an ovarian cancer HR of **0.31 (95% CI, 0.12–0.82)**. Among *BRCA1* carriers with previous breast cancer, the corresponding HR was **0.15 (95% CI, 0.04–0.63)**. No ovarian cancer events were observed among *BRCA2* carriers without previous breast cancer who underwent salpingo-oophorectomy during approximately six years of prospective follow-up, whereas ovarian cancer was documented among women retaining their ovaries (Domchek et al., 2010).

The mortality analyses also showed consistent point estimates when stratified by age. In an exploratory analysis, all-cause mortality was associated with an HR of **0.41 (95% CI, 0.25–0.67)** among women younger than 50 years and **0.37 (95% CI, 0.15–0.94)** among those aged 50 years or older. The interaction between age group and mortality benefit was not statistically significant in the original analysis, indicating that the study did not demonstrate a clear difference in the association according to these age categories (Domchek et al., 2010).

The findings represented in Figure 5 are also consistent with earlier prospective evidence evaluating ovarian, fallopian tube, and primary peritoneal cancer outcomes after prophylactic bilateral salpingo-oophorectomy. In a cohort of 1,828 *BRCA1/2* carriers, bilateral oophorectomy was associated with an adjusted hazard ratio of **0.20 (95% CI, 0.07–0.58)** for ovarian, fallopian tube, or peritoneal cancer, corresponding to an estimated **80% reduction in relative cancer risk**. The study recorded an incidence of 1,015 cases per 100,000 person-years among women with intact ovaries compared with 217 per 100,000 person-years following prophylactic oophorectomy.

Taken together, the quantitative results displayed in Figure 5 show consistently lower hazard estimates among women undergoing risk-reducing salpingo-oophorectomy across all analyzed outcomes. Relative hazard reductions calculated from the reported point estimates were approximately **86% for ovarian cancer among women with previous breast cancer, 72% for ovarian cancer among women without previous breast cancer, 60% for all-cause mortality, 56% for breast cancer-specific mortality, and 79% for ovarian cancer-specific mortality**.

DISCUSIÓN

The findings of this study demonstrate that hereditary gynecologic cancer cannot be adequately understood as a single category of inherited malignancy. Instead, the reviewed evidence reveals substantial heterogeneity according to the affected gene, the organ at risk, age, family history, and the preventive intervention considered. The quantitative patterns observed across the five figures support a model in which hereditary cancer susceptibility exists along a continuum ranging from high-penetrance conditions, particularly those involving *BRCA1*, to moderate-penetrance susceptibility associated with genes such as *BRIPI*, *RAD51C*, and *RAD51D*. At the same time, the Lynch syndrome findings demonstrate that considerable heterogeneity can exist even among genes belonging to the same hereditary syndrome. This genetic diversity has important consequences for clinical identification, counseling, risk estimation, and preventive decision-making.

One of the clearest findings was the difference in ovarian cancer penetrance between *BRCA1* and *BRCA2*. The cumulative ovarian cancer risks of approximately 44% and 17%, respectively, demonstrate that classification under the common category of hereditary breast and ovarian cancer syndrome should not imply equivalent clinical risk. Kuchenbaecker et al. (2017) similarly demonstrated that cancer risk varies according to both the affected *BRCA* gene and additional variables such as family history and mutation position. These findings reinforce the importance of gene-specific risk estimates rather than treating the presence of any pathogenic *BRCA1/2* variant as a uniform predictor of ovarian cancer occurrence.

The contrast becomes even more relevant when *BRCA1/2* are compared with moderate-penetrance genes. The cumulative risks represented for *RAD51C*, *RAD51D*, and *BRIPI* were substantially lower than the estimate for *BRCA1*, although they remained above general-population ovarian cancer risk. This gradient supports the increasing transition from binary genetic models toward personalized absolute-risk assessment. The 2025 ACMG clinical practice resource

explicitly classifies *RAD51C*, *RAD51D*, and *BRIP1* as moderate-penetrance ovarian cancer predisposition genes and emphasizes that their associated risks may be modified by family history and other factors. The same guidance recommends consideration of risk-reducing salpingo-oophorectomy close to the age of natural menopause, with timing based on age-specific risk and shared decision-making rather than automatically applying the earlier surgical thresholds typically considered for high-risk *BRCA1* carriers (Ngeow et al., 2025).

The findings related to Lynch syndrome further illustrate the limitations of syndrome-level classification without gene-level differentiation. The observed patterns showed that *MLH1*, *MSH2*, and *MSH6* do not produce identical gynecologic cancer profiles, while prospective evidence has demonstrated substantially lower or less clearly elevated cancer risks for *PMS2*. Data from 6,350 carriers and more than 51,000 prospective follow-up years showed that pathogenic *MLH1* and *MSH2* variants produce highly penetrant cancer syndromes with substantial endometrial and ovarian cancer risks, whereas *MSH6* is particularly characterized by a high endometrial cancer risk. The same study did not demonstrate a significantly increased overall cancer risk among *PMS2* carriers during the observed follow-up (Dominguez-Valentin et al., 2020).

This distinction is especially important for gynecology because endometrial cancer may constitute the first clinically recognized manifestation of Lynch syndrome. A patient presenting with an apparently isolated gynecologic malignancy may therefore be the first identifiable carrier within a family. Molecular evaluation of mismatch repair deficiency and microsatellite instability can expand detection beyond traditional pedigree-based criteria, particularly when family history is incomplete or uninformative. However, tumor abnormalities alone do not necessarily establish germline hereditary disease, which reinforces the need for confirmatory genetic evaluation and appropriate counseling.

The results concerning genetic testing revealed a different type of problem: the gap between available genomic knowledge and its implementation in routine oncology. Despite professional recommendations supporting genetic evaluation for ovarian cancer, the SGO reports that only about one third of affected patients complete germline or somatic genetic testing. This discrepancy is particularly relevant because ovarian cancer is one of the malignancies in which a molecular result may simultaneously influence hereditary risk assessment, treatment selection, and cascade testing of relatives (Gressel et al., 2024).

The implementation gap suggests that technological availability alone is insufficient to achieve precision prevention. Effective hereditary cancer programs require referral pathways, access to genetics services, appropriate interpretation of results, and mechanisms for communicating findings to patients and their relatives. NICE recommends formal referral pathways linking primary care, genetics, gynecologic oncology, and multidisciplinary familial cancer services. It also recommends cascade testing for appropriate relatives of individuals with known pathogenic variants and individualized ovarian cancer risk assessment incorporating age, family history, the specific pathogenic variant, and additional modifiers (NICE, 2024).

These recommendations are consistent with the central hypothesis of the present study: a pathogenic variant should not be interpreted independently from the clinical context in which it occurs. For example, two carriers of the same moderate-penetrance variant may have materially different absolute risks if their ages and family histories differ. NICE specifically advises the use of validated tools that combine variables such as age, family history, and pathogenic variant status and acknowledges additional factors—including parity, oral contraceptive use, and endometriosis—that may not be fully represented in simpler models. This reinforces the concept that hereditary cancer risk is probabilistic and multidimensional rather than determined by genotype alone.

Genetic counseling consequently emerges as a central clinical intervention rather than merely a procedural requirement before laboratory testing. Increasing use of multigene panels creates the possibility of identifying pathogenic variants outside the initially suspected syndrome, but it also increases the likelihood of variants of uncertain significance. The distinction is critical because a variant of uncertain significance should not be managed as though it were a pathogenic variant. Counseling provides the framework needed to communicate uncertainty, penetrance, residual risk, reproductive implications, familial consequences, and the differences between positive, negative, and inconclusive results. Its importance becomes greater as testing expands from highly penetrant genes toward genes for which absolute-risk estimates are still evolving.

The preventive surgery findings represented another major component of the results. Risk-reducing salpingo-oophorectomy among *BRCA1/2* carriers was associated with lower ovarian cancer occurrence as well as lower all-cause, breast cancer-specific, and ovarian cancer-specific mortality in the prospective cohort analyzed by Domchek et al. (2010). All-cause mortality was lower among women undergoing the procedure, with an HR of 0.40, while ovarian cancer-specific mortality was associated with an HR of 0.21. These observations support a strong association between preventive surgery and favorable cancer-related outcomes in appropriately selected high-risk carriers.

Nevertheless, the magnitude of benefit identified in *BRCA1/2* carriers should not be extrapolated without qualification to every hereditary cancer gene. The risk–benefit balance of surgery depends on baseline cancer probability, age at which risk begins to rise, reproductive status, and potential harms associated with premature loss of ovarian function. This distinction is particularly relevant for *RAD51C*, *RAD51D*, and *BRIP1*, for which current ACMG guidance supports risk-reducing salpingo-oophorectomy closer to natural menopause and emphasizes individualized decision-making. Therefore, the same preventive procedure may be appropriate at different ages depending on the susceptibility gene and personal risk profile (Ngeow et al., 2025).

The benefits of preventive surgery must also be considered alongside its non-oncologic consequences. Premenopausal bilateral oophorectomy produces abrupt estrogen deprivation and may affect vasomotor symptoms, sexual function, bone health, cardiovascular health, fertility, and quality of life. Consequently, the objective of hereditary cancer prevention should not be restricted to reducing cancer incidence at any cost. The timing and type of preventive intervention should instead seek an appropriate balance between expected oncologic benefit and the potential consequences of treatment, particularly in unaffected carriers who are otherwise healthy at the time preventive surgery is considered.

The findings additionally highlight the importance of cascade testing as a mechanism through which genetic diagnosis can extend prevention beyond the index patient. Identification of a germline pathogenic variant in an individual with cancer can allow relatives to undergo targeted testing before disease develops. Those who do not carry the familial variant may avoid hereditary syndrome-specific interventions, whereas carriers can receive individualized surveillance, counseling, and preventive options. NICE explicitly recommends genetic counseling and cascade testing for first-degree relatives of individuals with known pathogenic variants and, in selected circumstances, for more distant relatives when an intervening family member cannot be tested (NICE, 2024).

From a multidisciplinary perspective, the results therefore support integration among gynecologic oncology, medical genetics, pathology, reproductive medicine, primary care, and psychological support. Hereditary cancer management involves several sequential transitions: recognizing a suspicious clinical phenotype, selecting the appropriate molecular test, interpreting the result, communicating familial implications, estimating individual cancer probability, and deciding whether surveillance or preventive intervention is appropriate. Failure at any stage can prevent a theoretically actionable genetic finding from producing an actual preventive benefit.

Limitations

Several limitations should be considered when interpreting the present findings. First, the results were obtained from an integrative review rather than from a single uniform patient cohort. The quantitative estimates displayed across the figures originated from studies with different populations, inclusion criteria, follow-up periods, statistical methods, and genetic ascertainment strategies. Direct numerical comparison therefore provides a useful descriptive overview but should not be interpreted as a head-to-head comparison performed within one population.

Second, the precision of risk estimates differs substantially among genes. *BRCA1* and *BRCA2* have been studied in large international prospective cohorts, whereas moderate-penetrance genes are supported by smaller numbers of carriers and, in some studies, statistical modeling of family data. The wider confidence intervals observed for *RAD51C* and *RAD51D* reflect this uncertainty. ACMG has specifically identified the need for additional prospective data concerning clinical outcomes among carriers of *RAD51C*, *RAD51D*, and *BRIP1* pathogenic variants (Ngeow et al., 2025).

Third, the approximate one-third genetic-testing completion rate represented in the results should not be interpreted as a universal prevalence. It is a broad estimate summarized by the SGO, while individual healthcare systems and

specialized cancer centers may achieve considerably higher testing rates. Differences in healthcare access, referral systems, insurance coverage, geographic location, availability of genetic counselors, patient characteristics, and institutional testing models can modify uptake (Gressel et al., 2024).

Fourth, observational evidence regarding preventive surgery is susceptible to selection bias and residual confounding. Randomized assignment to risk-reducing salpingo-oophorectomy would pose substantial ethical and practical difficulties in individuals with known high-risk pathogenic variants; consequently, much of the evidence relies on prospective observational cohorts. Although the associations with reduced cancer incidence and mortality are substantial, the design must be considered when interpreting causality.

Implications and Future Research

Future research should prioritize prospective, gene-specific data collection, particularly for moderate-penetrance susceptibility genes and less common syndromes. Greater precision is required regarding age-specific penetrance, the influence of family history and polygenic modifiers, long-term outcomes of risk-reducing procedures, and the consequences of alternative strategies designed to delay menopause. Research should also examine methods for increasing uptake of germline testing, completion of cascade testing, and equitable access to genomic services.

A second priority is improving individualized risk prediction. Contemporary guidance already recognizes that pathogenic variant status alone is insufficient for several hereditary syndromes. Models incorporating gene, age, family history, reproductive factors, and potentially polygenic risk may allow preventive interventions to be timed more precisely. Such strategies may be especially valuable for moderate-penetrance genes, where the balance between cancer reduction and treatment-related consequences is less straightforward than for *BRCA1*.

Overall, the findings support an integrated model of hereditary gynecologic oncology in which **clinical phenotype, family history, molecular diagnosis, gene-specific penetrance, genetic counseling, and preventive intervention are interpreted as interconnected components of the same clinical pathway**. The principal contribution of this approach is not simply the identification of individuals carrying pathogenic variants, but the translation of inherited genomic information into proportionate and individualized prevention. The evidence analyzed in this study therefore supports a transition from syndrome-based management toward **gene-specific and patient-centered hereditary cancer prevention**, while emphasizing that the effectiveness of precision oncology ultimately depends on whether genetic knowledge can be translated into accessible, informed, and clinically appropriate action.

CONCLUSIÓN

Hereditary gynecologic cancer syndromes represent a clinically heterogeneous group of conditions in which inherited pathogenic variants confer substantially different risks according to the affected gene, the malignancy involved, age, family history, and individual clinical characteristics. The evidence analyzed in this study demonstrates that hereditary susceptibility should not be interpreted as a uniform category, even within the same syndrome. Differences observed between *BRCA1* and *BRCA2*, among mismatch repair genes associated with Lynch syndrome, and across moderate-penetrance genes such as *BRIP1*, *RAD51C*, and *RAD51D* confirm the importance of gene-specific risk assessment.

The results also support the central hypothesis of this study: the most clinically useful approach to hereditary gynecologic cancer is one that integrates personal and family history, molecular testing, gene-specific penetrance, genetic counseling, and individualized preventive strategies. Genetic information alone is insufficient if it is not translated into a structured clinical pathway capable of identifying high-risk individuals, interpreting molecular findings appropriately, and connecting those findings with surveillance, cascade testing, reproductive counseling, and risk-reducing interventions.

Genetic counseling emerged as a fundamental component of this process. Its role extends beyond communicating laboratory results and includes explaining inheritance patterns, residual risk, variants of uncertain significance, reproductive implications, potential consequences for relatives, and the benefits and limitations of preventive interventions. In this context, cascade testing represents a particularly important strategy because the identification of

a pathogenic germline variant in one individual can facilitate preventive evaluation in multiple relatives before the development of malignancy.

The analysis further demonstrated that risk-reducing surgery remains a major component of hereditary gynecologic cancer prevention, particularly among carriers of high-risk *BRCA1/2* variants. However, the timing and appropriateness of surgery must be individualized according to the gene involved, age-specific cancer risk, reproductive goals, family history, and the potential consequences of premature menopause. This consideration is especially important for moderate-penetrance genes, for which the magnitude and timing of risk differ from those observed in classical high-penetrance hereditary syndromes.

An important finding was the persistent gap between recommendations for genetic evaluation and actual completion of testing. The effectiveness of precision prevention therefore depends not only on the availability of genomic technologies but also on appropriate referral systems, access to genetic services, multidisciplinary collaboration, and mechanisms that facilitate interpretation and follow-up. Without these elements, potentially actionable genetic information may fail to produce meaningful preventive benefit.

REFERENCIAS

- American College of Obstetricians and Gynecologists. (2019). Hereditary cancer syndromes and risk assessment: ACOG Committee Opinion No. 793. *Obstetrics & Gynecology*, 134(6), e143–e149. doi:10.1097/AOG.0000000000003562.
- Crosbie, E. J., Ryan, N. A. J., Arends, M. J., Bosse, T., Burn, J., Cornes, J. M., Crawford, R., Eccles, D., Frayling, I. M., Ghaem-Maghani, S., Hampel, H., Kauff, N. D., Kitchener, H. C., Kitson, S. J., Manchanda, R., McMahon, R. F. T., Monahan, K. J., Menon, U., Møller, P., ... Evans, D. G. (2019). The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. *Genetics in Medicine*, 21(10), 2390–2400. doi:10.1038/s41436-019-0489-y.
- Dhawan, A., Baitamouni, S., Liu, D., Yehia, L., Anthony, K., McCarther, A., Tischkowitz, M., MacFarland, S. P., Ngeow, J., Hoogerbrugge, N., & Eng, C. (2025). Cancer and overgrowth manifestations of PTEN hamartoma tumor syndrome: Management recommendations from the International PHTS Consensus Guidelines Working Group. *Clinical Cancer Research*, 31(9), 1754–1765. doi:10.1158/1078-0432.CCR-24-3819.
- Domchek, S. M., Friebel, T. M., Singer, C. F., Evans, D. G., Lynch, H. T., Isaacs, C., Garber, J. E., Neuhausen, S. L., Matloff, E., Eeles, R., Pichert, G., Van't Veer, L., Tung, N., Weitzel, J. N., Couch, F. J., Rubinstein, W. S., Ganz, P. A., Daly, M. B., Olopade, O. I., ... Rebbeck, T. R. (2010). Association of risk-reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. *JAMA*, 304(9), 967–975. doi:10.1001/jama.2010.1237.
- Dominguez-Valentin, M., Sampson, J. R., Seppälä, T. T., Ten Broeke, S. W., Plazzer, J. P., Nakken, S., Engel, C., Aretz, S., Jenkins, M. A., Sunde, L., Bernstein, I., Capella, G., Balaguer, F., Thomas, H., Evans, D. G., Burn, J., Greenblatt, M., Hovig, E., de Vos Tot Nederveen Cappel, W. H., ... Møller, P. (2020). Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: Findings from the Prospective Lynch Syndrome Database. *Genetics in Medicine*, 22(1), 15–25. doi:10.1038/s41436-019-0596-9.
- Gressel, G. M., Frey, M. K., Norquist, B., Senter, L., Blank, S. V., & Urban, R. R. (2024). Germline and somatic testing for ovarian cancer: An SGO clinical practice statement. *Gynecologic Oncology*, 181, 170–178. doi:10.1016/j.ygyno.2023.12.010.
- Idos, G., & Valle, L. (2021). Lynch syndrome. In M. P. Adam, S. Bick, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle.
- Konstantinopoulos, P. A., Norquist, B., Lacchetti, C., Armstrong, D., Grisham, R. N., Goodfellow, P. J., Kohn, E. C., Levine, D. A., Liu, J. F., Lu, K. H., Sparacio, D., & Annunziata, C. M. (2020). Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline. *Journal of Clinical Oncology*, 38(11), 1222–1245. doi:10.1200/JCO.19.02960.
- Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K. A., Mooij, T. M., Roos-Blom, M. J., Jervis, S., van Leeuwen, F. E., Milne, R. L., Andrieu, N., Goldgar, D. E., Terry, M. B., Rookus, M. A., Easton, D. F., Antoniou, A. C., McGuffog, L., Evans, D. G., Barrowdale, D., Frost, D., ... Olsson, H. (2017). Risks of

breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA*, 317(23), 2402–2416. doi:10.1001/jama.2017.7112.

- Liu, Y. L., Breen, K., Catchings, A., Ranganathan, M., Latham, A., Goldfrank, D. J., Grisham, R. N., Long Roche, K., Frey, M. K., Chi, D. S., Abu-Rustum, N., Aghajanian, C., Offit, K., & Stadler, Z. K. (2022). Risk-reducing bilateral salpingo-oophorectomy for ovarian cancer: A review and clinical guide for hereditary predisposition genes. *JCO Oncology Practice*, 18(3), 201–209. doi:10.1200/OP.21.00382.
- McGarrity, T. J., Amos, C. I., & Baker, M. J. (2021). Peutz-Jeghers syndrome. In M. P. Adam, S. Bick, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle.
- National Comprehensive Cancer Network. (2026). *Genetic/familial high-risk assessment: Breast, ovarian, pancreatic, and prostate (Version 2.2026)*. NCCN Clinical Practice Guidelines in Oncology.
- Ngeow, J., Chiang, J., Astiazaran-Symonds, E., Balmaña, J., Cass, I., Kommoss, F. K. F., Foulkes, W. D., James, P. A., Katcher, A., Klugman, S., Livinski, A. A., Mak, J. S., Voian, N., Wick, M. J., Tischkowitz, M., Pal, T., Stewart, D. R., & Hanson, H. (2025). Management of individuals with heterozygous germline pathogenic variants in RAD51C, RAD51D, and BRIP1: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genetics in Medicine*, 27(11), 101557. doi:10.1016/j.gim.2025.101557.
- National Institute for Health and Care Excellence. (2024). *Ovarian cancer: Identifying and managing familial and genetic risk (NICE Guideline NG241)*. National Institute for Health and Care Excellence.
- Petrucelli, N., Daly, M. B., & Pal, T. (2026). BRCA1- and BRCA2-associated hereditary breast and ovarian cancer. In M. P. Adam, S. Bick, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle.
- Schmeler, K. M., Lynch, H. T., Chen, L. M., Munsell, M. F., Soliman, P. T., Clark, M. B., Daniels, M. S., White, K. G., Boyd-Rogers, S. G., Conrad, P. G., Yang, K. Y., Rubin, M. M., Sun, C. C., Slomovitz, B. M., Gershenson, D. M., & Lu, K. H. (2006). Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *The New England Journal of Medicine*, 354(3), 261–269. doi:10.1056/NEJMoa052627.
- Schultz, K. A. P., Nelson, A. T., Kamihara, J., Bauer, A. J., Hatton, J., Merideth, M. A., Stratton, P., Harris, A. K., Field, A., Dehner, L. P., Stewart, D. R., Hill, D. A., & Messinger, Y. H. (2026). DICER1-related tumor predisposition. In M. P. Adam, S. Bick, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle.
- Steenbeek, M. P., Harmsen, M. G., Hoogerbrugge, N., Arts de Jong, M., Maas, A. H. E. M., Prins, J. B., Bulten, J., Teerenstra, S., van Bommel, M. H. D., van Doorn, H. C., Mourits, M. J. E., van Beurden, M., Zweemer, R. P., Gaarenstroom, K. N., Slangen, B. F. M., Brood-van Zanten, M. M. A., Vos, M. C., Piek, J. M. J., van Lonkhuijzen, L. R. C. W., ... de Hullu, J. A. (2021). Association of salpingectomy with delayed oophorectomy versus salpingo-oophorectomy with quality of life in BRCA1/2 pathogenic variant carriers: A nonrandomized controlled trial. *JAMA Oncology*, 7(8), 1203–1212. doi:10.1001/jamaoncol.2021.1590.
- Suszynska, M., Ratajska, M., & Kozlowski, P. (2020). BRIP1, RAD51C, and RAD51D mutations are associated with high susceptibility to ovarian cancer: Mutation prevalence and precise risk estimates based on a pooled analysis of ~30,000 cases. *Journal of Ovarian Research*, 13, 50. doi:10.1186/s13048-020-00654-3.
- Tramontana, T., & Yehia, L. (2026). PTEN hamartoma tumor syndrome. In M. P. Adam, S. Bick, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle.