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REVIEW

Hereditary Breast, Ovarian, Pancreatic and Prostate Cancer Syndrome: Multigene Testing, Multiomics, and Risk Management

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SUMMARY

Hereditary breast, ovarian, pancreas and prostate cancer (HBOC/HBOPC) syndromes remain a major global health concern, with *BRCA1*, *BRCA2* and other high- or moderate-risk homologous recombination repair (HRR) gene variants driving a significant share of familial cancer risk. Beyond breast and ovarian sites, these mutations increase susceptibility to prostate, pancreatic, and other solid tumors, highlighting the syndromic nature of HBOPC. Advances in multigene panel testing (MPT), AI-supported variant classification, and polygenic risk scores (PRS) now enable more precise risk estimation, while functional reclassification and population-specific founder mutation mapping reduce uncertainty in underrepresented groups. Emerging epigenetic and non-coding RNA biomarkers further strengthen early detection and treatment stratification. However, large-scale validation is still needed to translate these tools into equitable care. Risk-reducing surgeries, tailored surveillance, and targeted therapies—including PARP inhibitors, immunotherapy, and homologous recombination deficiency (HRD)-based regimens—have transformed management but require equitable access and culturally sensitive counseling to address psychosocial barriers and family communication challenges. Real-world data (RWD) and cross-border variant databases are essential to bridge gaps between guidelines and practice, especially where founder effects and mosaicism complicate standard criteria. This review integrates current evidence on the genetic and molecular foundations, organ-specific management, evolving therapies, and ethical dimensions of HBOPC care. By combining multidisciplinary insights with AI, functional analyses, and real-world implementation strategies, this review highlights how next-generation precision oncology can deliver equitable, high-quality, and locally adapted prevention and treatment for families worldwide.

Keywords: *BRCA1 & BRCA2*; founder mutations; hereditary breast ovarian pancreatic prostate cancer syndrome; multigene panel; polygenic risk score; precision oncology.

INTRODUCTION

Cancer remains one of the most critical public health burdens of the 21st century, driven by rising incidence and mortality rates worldwide. According to GLOBOCAN 2022 estimates, approximately 20 million new cases are diagnosed globally each year, resulting in nearly 9.7 million cancer-related deaths. Consequently,

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one in five individuals is expected to develop malignancy during their lifetime.[1] Among all neoplasms, breast cancer (BC) is the most prevalent malignancy in women, with 2.3 million new cases annually, representing nearly a quarter of all female cancer diagnoses. In comparison, ovarian cancer (OC) accounts for around 324,000 new cases and 207,000 deaths per year, ranking it among the leading gynecological cancers.[1]

It is generally estimated that 5–10% of all cancers have a hereditary basis.[2,3] Nonetheless, considering the two-hit hypothesis along with additional genetic, epigenetic, and environmental factors, the true contribution of hereditary risk likely to exceed this estimate.[4–7] Among hereditary cancers, HBOPC and Lynch syndrome (LS) are the most extensively characterized and together account for a substantial fraction of inherited malignancies.[3,8] Pathogenic variants in *BRCA1* and *BRCA2*, which play a pivotal role in HRR pathways, underlie the genetic basis of HBOPC and confer significantly increased risks of breast, ovarian, prostate, and pancreatic cancers.[9–13] While *BRCA1*/*BRCA2* genes remain central, non-BRCA genes such as *PALB2, ATM, CHEK2, TP53*, and mismatch repair (MMR) genes associated with LS (*MLH1, MSH2, MSH6, PMS2*) further broaden the spectrum of hereditary cancer risk. Notably, the introduction of MPT has greatly improved diagnostic yield by covering this expanded genetic landscape.[14–17]

Recent advancements in multigene panels, AI-assisted variant classification, and PRS have markedly refined individualized risk prediction and early detection.[2,14,18–20] Simultaneously, advances in functional assays, founder mutation analyses, and emerging epigenetic and non-coding RNA biomarkers have expanded our understanding of population-specific variant spectra and therapeutic targets.[6,7,21–25] Nevertheless, real-world evidence consistently reveals that psychosocial barriers, family communication gaps, and unequal access to counseling and testing continue to limit the full potential of these advances—particularly for low-resource and underrepresented groups.[11,26–29]

This review synthesizes current evidence on HBOPC and related hereditary syndromes by examining their genetic and epigenetic underpinnings, real-world founder mutation patterns, organ-specific risks, risk-reducing interventions, and emerging therapeutic avenues such as PARP inhibitors (PARPi) and immunotherapy. Additionally, it highlights the ethical and psychosocial dimensions that shape uptake of testing and cascade screening. By integrating AI-enabled tools, real-world datasets, and regionally tailored approaches, this work aims to equip multidisciplinary teams to translate precision oncology advances into practical, equitable, and culturally responsive care for diverse populations (Fig. 1). In line with the most recent NCCN guidelines, which expanded the Genetic/Familial High-Risk Assessment beyond breast and ovarian to also include pancreatic and prostate cancers,[30] we consistently use the broader term HBOPC (Hereditary Breast, Ovarian, Pancreatic and Prostate Cancer) throughout this review. This choice is further supported by recent literature that has adopted the same terminology in clinical and research contexts.[31–33] Where the older term HBOC is found, it reflects historical usage in cited references rather than our framework.

GENETICS AND MOLECULAR BASIS

BRCA1/BRCA2 Mutations: Spectrum, Penetrance, and Therapeutic Response

BRCA1 and *BRCA2* are key tumor suppressor genes that play a pivotal role in homologous recombination (HR)-mediated DNA repair. Loss of function—whether through pathogenic variants or epigenetic silencing—induces HRD, which leads to genomic instability and increased susceptibility to multiple cancer types.[16,17,34,35] Estimated lifetime risks for BC in *BRCA1* carriers range from 60% to 72% (HR, 95% CI 58–74) and from 55% to 69% for *BRCA2* (HR, 95% CI 52–71), while OC risks range from 39% to 58% for *BRCA1* (HR, 95% CI 36–60) and 11% to 25% for *BRCA2* (HR, 95% CI 9–27). Importantly, *BRCA1*/*BRCA2* mutations are also associated with elevated risks for prostate (RR ~3.5, 95% CI 2.8–4.4), pancreatic, (RR ~6.0, 95% CI 4.0–8.5), melanoma (OR ~2.6, 95% CI 1.8–3.7), and male breast cancers (RR ~15, 95% CI 10–22), with these risks comprehensively outlined in Table 1.[17,36] Consequently, *BRCA1*/*BRCA2* mutations remain the best-characterized genetic basis of HBOPC.

Population-based analyses highlight substantial variability in *BRCA1/BRCA2* mutation frequencies and associated cancer risks across different ethnicities and regions. A notable example is the UK Biobank, which shows that *BRCA2* mutations increase risk not only for breast and ovarian cancers but also for prostate, pancreatic, melanoma and other solid tumors, with female BC risk reaching 29.2% (HR 4.89, 95% CI 4.32–5.54) and a 15-fold increase for male BC (HR 15.42, 95% CI 7.20–33.01).[37] Prostate cancer

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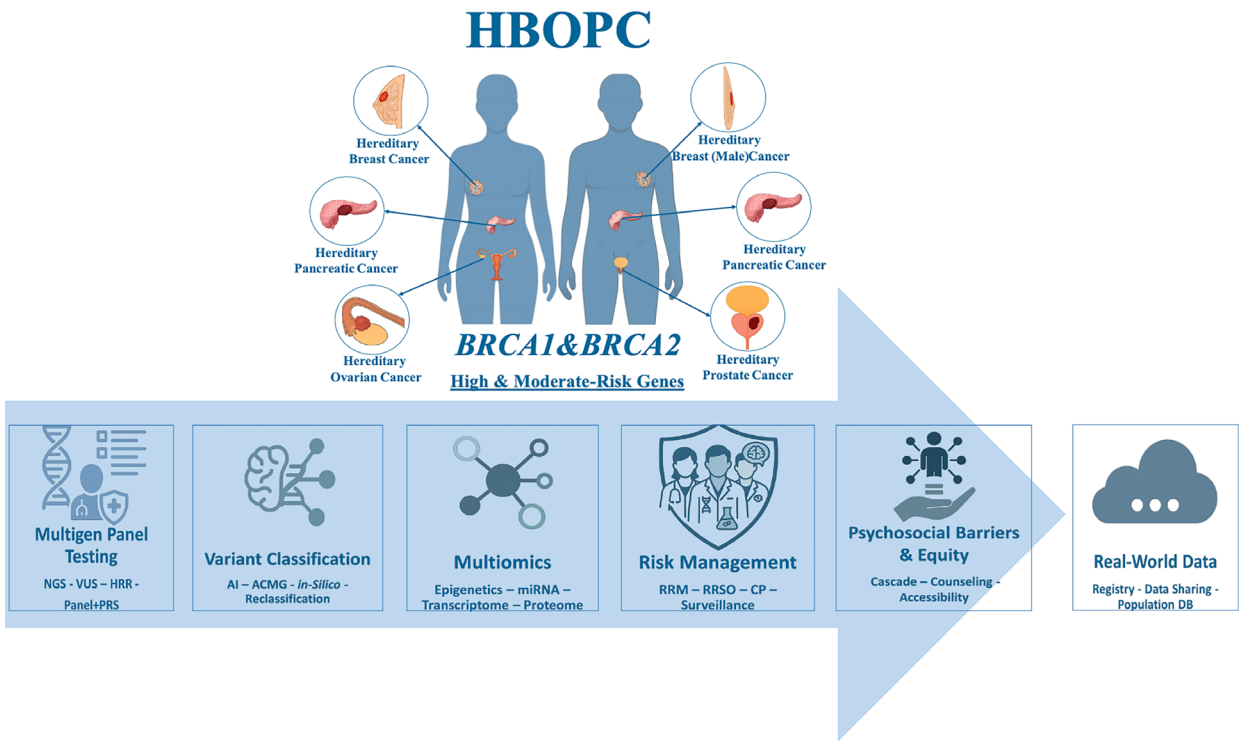

Fig. 1. Schematic overview of the hereditary breast, ovarian, pancreas and prostate cancer (HBOPC) spectrum, associated organ-specific risks, and the integrated multidimensional management approach, illustrated as a simplified roadmap of future pathways.

NGS: Next-Generation Sequencing; VUS: Variants of Uncertain Significance; HRR: Homologous Recombination Repair; PRS: Polygenic Risk Score; AI: Artificial Intelligence; ACMG: American College of Medical Genetics; in-silico, Computational Prediction; RRM: Risk-Reducing Mastectomy; RRSO: Risk-Reducing Salpingo-Oophorectomy; CP: Chemoprevention; Cascade, Cascade Testing; RWD: Real-World Data; Registry, Patient Registries; Population DB: Population-Based Variant Databases.

risk in male *BRCA2* carriers may reach as high as 60% (lifetime risk 60%, 95% CI 43–78%),[38] further underscoring the importance of comprehensive genetic counseling and cascade testing to optimize early detection and prevention.[27]

There is strong evidence that *BRCA1/BRCA2* pathogenic variants are associated with distinct tumor subtypes. *BRCA1* mutations are detected in over 50% of triple-negative breast cancer (TNBC) cases, whereas *BRCA2* mutations are more frequently linked to estrogen receptor–positive (ER+) phenotypes.[7,22,39,40]

Recent genetic studies show that PRS can significantly modify the penetrance of monogenic variants. For example, high-PRS *BRCA1/BRCA2* carriers may have BC risks approaching 76% (95% CI 72–80) by age 75, highlighting the benefit of integrating PRS into personalized risk estimation and screening strategies.[20,23]

Emerging data suggest that *BRCA1/BRCA2* variants may shape treatment response through molecular features such as HRD status and tumor immune microenvironment changes. These molecular profiles may modulate PD-L1 expression and support the rationale for combining PARPi with immunotherapy.[41]

Emerging findings indicate that psychosocial barriers can significantly influence the uptake of genetic testing and cascade screening. Fear of genetic discrimination contributes to suboptimal completion rates, while genetic labeling anxiety may impose a psychosocial burden regardless of objective penetrance.[27,28]

Taken together, these data on the mutation spectrum, penetrance, and molecular phenotypes of *BRCA1/BRCA2* variants form the cornerstone for advancing individualized risk assessment and tailored management in HBOPC.

Non-*BRCA1/BRCA2* High- and Moderate-Risk Genes and Candidate Genes

Beyond *BRCA1* and *BRCA2*, several other high- and moderate-penetrance genes significantly contribute

to the genetic basis of HBOPC syndromes. Estimated lifetime risks, syndromic associations, founder mutations, and management highlights for these genes are detailed in Table 1.[17] Pathogenic variants (PVs) in high-penetrance genes such as *TP53, PALB2, STK11, PTEN,* and *CDH1* are linked to distinct hereditary cancer syndromes—including Li-Fraumeni, Peutz-Jeghers, and hereditary diffuse gastric cancer (HDGC)—and often confer increased risks of aggressive tumor phenotypes and multi-organ involvement at an early age, with lifetime BC risks ranging from ~40% to 80% (e.g., *TP53* ~80%, 95% CI 70–90; *PALB2* 44–60%, HR 4.5, 95% CI 3.5–5.6; CDH1 40–50%).[17,42,43]

Population-based studies indicate that among moderate-risk genes, *CHEK2, ATM, BARD1, RAD51C, RAD51D*, and *NBN* are particularly noteworthy. Although variants in these genes do not always strongly correlate with BRCA-like phenotypes, their clinical relevance increases when combined with family history, age, tumor subtype, or PRS.[22,39] Reported mutation rates for *CHEK2* reach up to 12.2% (OR ~2.3; 95% CI 1.8–2.9) and for *ATM* up to 5.6% (HR ~2.0; 95% CI 1.4–2.7) in certain cohorts. Variants in *BARD1, RAD51C, RAD51D*, and *NBN* are less frequent (typically 1–2%), but their contribution is clinically meaningful in the presence of family history or *TNBC* predisposition. It is also emphasized that there is no established direct association between *PALB2* and the prevalence of *TNBC* within certain cohorts.[22]

There is growing evidence that the *MMR* genes—*MLH1, MSH2, MSH6*, and *PMS2*—linked to LS remain diagnostically relevant for endometrial and ovarian cancers.[44–46] Founder mutations in *MSH6* have been identified among Ashkenazi Jewish (AJ) individuals, highlighting how population-specific variants can guide targeted screening strategies.[47]

MPT has expanded the detection of *ATM, CHEK2*, *PALB2, RAD51C/D*, and *BARD1* variants among BRCA-negative cases.[14,15] Recent analyses have also identified PVs in candidate genes such as *DROSHA, SLC34A2*, and *FAN1*, which are involved in DNA repair pathways.[15] However, the clinical significance of certain candidate genes, including *MRE11A*, remains unconfirmed in systematic studies.[48] Family-based reports continue to highlight novel variants of uncertain significance (VUS). Such as, Biswas et al.[49] described a *BRCA*-negative Indian family in which a germline *RAD51D* variant co-segregated with four other incidental variants (*ADAMTS13, SYCE1, LIAS, PDHA1*), underscoring the complexity of moderate-risk gene interactions and the importance of cautious interpretation when assessing familial cancer predisposition and potential candidate risk modifiers.[49]

Emerging insights indicate that non-*BRCA1/BRCA2* genes are closely tied to HRR pathways, contributing to the BRCAness phenotype and informing molecularly targeted treatment approaches. For example, *ATM* mutations may create synthetic lethality opportunities when co-targeted with *ATR* or DNA-PKcs inhibitors.[50]

At the epigenetic level, recent evidence also shows that these genes can be regulated by miRNA pathways. For instance, Tuncer et al.[51] described the involvement of *TP53* and *CHEK2* in cell cycle control through the MDM2–CHEK1 axis, while Ghafour et al.,[52] Saral et al.[53] and Delek et al.[54] highlighted these specific miRNAs may modulate OC progression.[51–54]

Recognizing these non-*BRCA1/BRCA2* risk genes provides a critical framework for precision screening and tailored genetic counseling in diverse populations.

Founder Mutations, Variants of Uncertain Significance (VUS), and Epigenetic Modifiers

Variants of Uncertain Significance (VUS): VUS remain a major source of clinical ambiguity in HBOPC syndromes. By definition, these are genetic variants with unresolved pathogenicity. Carrier rates vary substantially depending on population diversity, panel scope, and classification algorithms, with estimates reaching up to 30% for *BRCA1/BRCA2* in large cohorts.[23] Elevated VUS rates have also been reported for moderate-risk genes such as *ATM* and *CHEK2*.[22] Notably, underrepresented populations often show disproportionately higher VUS rates due to limited reference data, as clearly demonstrated in the Caribbean cohort, where the VUS prevalence reached 33%.[39] In contrast, a Tanzanian cohort showed a remarkably low VUS rate of just 1%, highlighting regional variability.[55]

Emerging evidence shows that advances in functional reclassification are improving VUS interpretability. Tools such as RNA-splice assays, loss of heterozygosity (LOH) analyses, and AI-supported scoring (e.g., MAF, CADD, Eigen) now enable detection of splicing anomalies and structural variants affecting gene function.[10,50] For instance, the *BRCA1* c.5407-25T>A variant displays a "leaky splice" profile producing partially functional transcripts, while BRIP1 c.1140+1G>C demonstrates clear loss of function through exon skipping.[56] Integrating BRCAness features and LOH signatures into analysis pipelines may resolve a substantial portion of ambiguous findings.[10]

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Population-Specific Founder Mutations: Understanding population-specific founder mutations is crucial for refining testing strategies and contextualizing VUS findings. Estimated frequencies and founder variants are presented in Table 1.[17] Founder mutations, which arise from common ancestors and persist at high frequencies in genetically isolated groups, can significantly improve the cost-effectiveness and yield of MPT. The Ashkenazi Jewish community remains the best-known example, with carrier rates over threefold higher for *BRCA2* compared to the general population.[37] Similar effects have been observed in the Caribbean, where the prevalence of *BRCA1/2* pathogenic variants reached 23% in the Bahamas, reflecting a strong founder effect.[39] Additional regional clusters, such as *BRCA2* Tokushima-specific variants in Japan and the *BRCA1* c.3607C>T variant in Romania, emphasize the value of customized panels.[7,21,57]

At a more granular level, founder mutations can cluster within families or tribal groups. For example, a RAD51D variant has been documented segregating within an Indian family,[49] while a PMS2 exon 6–11 deletion has been identified in a tribal group in Qatar.[58] Regional differences have also been noted within Türkiye: *BRCA1/BRCA2* rearrangement frequencies unique to the Black Sea and Marmara regions highlight possible local founder effects and an increased prevalence of male BC.[59,60] However, translating these insights into equitable clinical practice remains challenging. Underrepresented or disadvantaged communities often face barriers in accessing genetic services; for example, chatbot-based engagement tools have shown significantly lower uptake among Hispanic individuals, underscoring the need for equitable outreach and culturally tailored genetic counseling.[11,61]

Epigenetic Modifiers and Non-Coding RNAs: Epigenetic modifiers add an intersecting layer by modulating the functional expression of both common and founder variants and clarifying ambiguous VUS results. DNA methylation patterns, such as *RASSF1A* or *CYB5R4* hypermethylation, have been linked to increased HBOPC risk and early diagnostic potential.[24,62,63] A case in point is promoter methylation of *RASSF1A*, which may be detectable in plasma DNA prior to diagnosis, supporting its potential as a non-invasive biomarker.[62]

Histone modifications are also influential. Loss of *BRCA1* can activate LSD-1–mediated H3K4me1/2 demethylation, HDAC1/2 activity, and proto-oncogene upregulation, reshaping the tumor microenvironment and promoting resistance mechanisms.[6,17]

Non-coding RNAs (ncRNAs) further refine this axis. Upregulated miRNAs such as miR-3135b, miR-1273g-3p, miR-3653-3p, and the miR-1260 family modulate DNA repair and cell cycle pathways.[51,52,54] Additionally, lncRNAs like HOTAIR and PANDAR interact with histone-modifying complexes to silence tumor suppressor genes, supporting multi-omic profiling as a promising tool for VUS reclassification and more accurate risk estimates.[6]

Taken together, these findings demonstrate that the integration of founder mutation mapping, advanced VUS reclassification, and multi-layered epigenetic profiling provides a clear framework to enhance HBOPC diagnostic precision and personalized risk prediction. Expanding population-specific variant databases, harmonizing data sharing, and validating new biomarkers will be key to realizing the full clinical potential of these mechanisms.

CLINICAL SYNDROMES AND ORGAN-SPECIFIC MANAGEMENT

Comprehensive Management of Hereditary Breast Cancer

Genetic and Phenotypic Risk Profile: Hereditary breast cancer (HBC) represents a unique clinical entity primarily driven by high- and moderate-risk genes such as *BRCA1, BRCA2, PALB2, TP53*, and *CHEK2*, which distinguish it from sporadic cases by features including earlier age of onset, bilateral disease risk, distinctive tumor subtype distribution, and increased male BC incidence.[22,43] Risk estimates, syndromic associations, founder variants, and key management highlights for these genes are compiled in Table 1 (95% CI, HR/OR as appropriate; EMQN, ASCO, ESMO);[16,17,34] Classic indicators include early-onset, bilateral tumors, or male BC, but large-scale analyses such as the 100,000 Genomes Project show that relying solely on phenotypic triggers may miss up to 20–30% of carriers.[23] Founder mutations and population-specific variants remain practical considerations; for example, in Bahamian populations, the prevalence of *BRCA1/2* pathogenic variants has been reported as high as 23%, underlining the value of founder-specific panels.[39] Mosaicism, low variant allele frequency (VAF) variants, and epigenetic markers such as *RASSF1A* or *CYB5R4* hypermethylation can further refine risk estimates.[24,62,63]

Screening and Surveillance Protocols: Genetic counseling forms the cornerstone of risk assessment and surveillance planning. International guidelines

EMQN;[17], ESMO;[16], ASCO;[34] emphasize comprehensive pre- and post-test counseling that includes variant interpretation, psychosocial impact, and cascade testing pathways to reach at-risk relatives, while addressing persistent barriers such as cost concerns, fear of positive results, and genetic discrimination. [27,29] Screening recommendations must align with gene-specific risk levels and tumor biology. For *BRCA1/BRCA2* carriers, annual breast MRI is recommended starting at ages 25–30, with mammography added after 30 while minimizing radiation exposure in young women due to theoretical radiosensitivity. [17,64] In Li-Fraumeni syndrome (*LFS*; *TP53*), therapeutic or diagnostic radiation warrants special caution as it can elevate sarcoma risk.[42] The strong association of TNBC with *BRCA1*—with prevalence reaching 53–57% in carriers under age 40 [22]—supports early and intensive MRI surveillance. Additionally, PRS can help tailor surveillance intervals by refining lifetime risk estimates.[20]

Risk-Reducing Surgery and Chemoprevention: Risk-reducing surgery, including prophylactic bilateral mastectomy (PBM) and contralateral prophylactic mastectomy (CPM), remains one of the most effective interventions for mutation carriers. For example, Guzauskas et al.[65] estimated PBM uptake rates to range between 15–36% in real-world settings, highlighting the influence of personal risk perception and clinical guidance on these decisions.[65] Among *BRCA1/BRCA2* carriers with unilateral disease, Makhnoon et al.[66] reported that 56% choose CPM, with post-CPM survival differences observed by race and ethnicity.[66] Real-world adoption is strongly influenced by psychosocial, cultural, and access-related factors.[61] Shared decision-making models, including tools like RealRisks and chatbot-based support, have shown promise in improving patient understanding and alignment with their values.[67] When surgery is deferred or declined, chemoprevention with selective estrogen receptor modulators (SERMs) such as tamoxifen or raloxifene remains an option to reduce incidence, although Trivedi et al.[68] emphasize that side effects and persistent hesitancy continue to limit broader uptake.[68]

Epigenetic and Molecular Modifiers: Emerging evidence highlights that HRD and structural variant burden (SVhigh) are critical factors in selecting candidates for PARPi therapy. Trials such as OlympiA and VELIA demonstrate that maintenance olaparib significantly improves progression-free survival in high-risk groups.[22] Optical genome mapping studies confirm that *BRCA1/BRCA2*-associated tumors with high HRD scores and SVhigh profiles may benefit from PARPi–immunotherapy combinations, leveraging pathways such as STING activation and PD-L1 upregulation. [9] Nonetheless, resistance mechanisms—including PRIMPOL-mediated replication fork stabilization and MYC/E2F1 amplification—emphasize the need for continuous tumor profiling, LOH analysis, and dynamic reclassification of VUS.[69]

Multidisciplinary Coordination and Best Practice Alignment: Guideline convergence from EMQN, ESMO, and ASCO underscores the importance of integrating MPT, founder variant mapping, PRS calculation, epigenetic profiling, and HRD/SVhigh data into patient-centered genetic counseling. Ensuring equitable access, adequately trained genetic counselors, and culturally sensitive communication remains essential to maximize uptake and align decisions with patient preferences.[16,17,34]

Managing HBC calls for a truly integrated approach that brings together gene-specific risk assessment, detailed molecular profiling, tailored risk-reducing strategies, and vigilant surveillance. As evidence on PARP inhibitor combinations, immunotherapy, and dynamic variant reclassification continues to expand, multidisciplinary teams must remain responsive and proactive—ensuring that the promise of precision medicine is realized as meaningful survival gains for patients across diverse populations.

Comprehensive Management of Hereditary Ovarian Cancer

Genetic Landscape and Counseling: Hereditary ovarian cancer is predominantly driven by *BRCA1/BRCA2* mutations, alongside contributions from HRR genes such as *RAD51C, RAD51D*, and *BRIP1*.[12,22,49,70] Risk estimates, syndromic associations, founder variants, and age-specific recommendations for these genes are outlined in Table 1 (95% CI, HR/OR as appropriate).[16,17,34] *BRCA1* carriers face an elevated risk for high-grade serous carcinoma (HGSC) after age 40, while *BRCA2* carriers tend to develop later-onset disease with lower penetrance.[37] Comprehensive genetic counseling forms the cornerstone of risk assessment and shared decision-making. Major guidelines (ESMO, EMQN, ASCO) recommend that counseling sessions address fertility preservation, hormone replacement therapy (HRT), and cascade testing for family members.[27,29] The wider use of multigene panels continues to uncover moderate-risk genes whose penetrance and clinical relevance require further validation.[49]

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Surgical Risk Reduction and Surveillance: In the absence of reliable early detection tools, risk-reducing salpingo-oophorectomy (RRSO) remains the most effective preventive strategy for high-risk carriers. EMQN and ESMO guidelines recommend RRSO between ages 35–40 for *BRCA1* and 40–45 for *BRCA2* carriers, aligned with age-specific HGSC risk.[16,17] Real-world uptake is variable: Guzauskas et al.[65] estimate that RRSO could prevent up to 8 cases per 100,000, yet Nazareth et al.[61] report that only 17% of eligible carriers undergo surgery, reflecting psychosocial and fertility-related concerns.[61,65] Surveillance options remain limited, as transvaginal ultrasound (TVUS) and CA-125 have not demonstrated a mortality benefit, reinforcing the importance of informed decision-making and consistent follow-up.[16] Notably, emerging biomarkers—such as *CYB5R4* hypermethylation and circulating miRNAs including miR-3135b, miR-1273g-3p, and miR-1260—may enhance early detection and monitoring of recurrence.[24,51,54,63,71]

Histology-Specific Insights and Imaging: Histological subtype remains a key factor in guiding genetic testing and treatment. *BRCA1/BRCA2* mutations are mostly linked to serous tumors, while LS-related MMR genes (*MSH2, MLH1, MSH6, PMS2*) can be found in clear cell and endometrioid subtypes.[44,46] MSI-H/MMR-D status predicts immunotherapy responsiveness, expanding treatment options beyond platinum-based chemotherapy and PARPi.[44] Although TVUS continues to be the standard for surveillance, its low sensitivity highlights surgical prevention as the mainstay. Digital tools and reminder systems may indirectly support follow-up and adherence.[61,67]

Therapeutic Approaches and Molecular Profiling: Treatment approaches increasingly integrate HRD status and detailed molecular profiling to optimize outcomes. Trials such as OlympiA and SOLO demonstrate significant survival benefits with PARPi maintenance therapy in *BRCA1/BRCA2* and HRD-positive ovarian cancers.[16,34] Recent evidence suggests that SVhigh tumors with high HRD scores may benefit from combined PARPi and immunotherapy regimens, driven by STING pathway activation and PD-L1 upregulation.[9] Rare histologies with high tumor mutational burden (TMB) or MSI-H/MMR-D features—including carcinosarcomas or clear cell variants with *POLE* mutations—may also respond to checkpoint inhibitors.[72] Molecular profiling tools—such as SV burden analysis, BRCAness features, and LOH signatures—refine treatment selection, while PRS may further support risk prediction when combined with monogenic and founder-specific data.[10,37]

Best Practices and Future Directions: Consensus across major guidelines (ESMO, EMQN, ASCO) underscores the need for broader panel testing, timely RRSO, and integration of HRD and MSI status into treatment planning. Proactive counseling is critical to address psychosocial barriers and promote adherence. Local implementation should adapt to population-specific factors, such as founder mutations—e.g., the 23% *BRCA1/2* prevalence in the Bahamas—and disparities in genetic testing uptake.[11,39]

Effective management of hereditary ovarian cancer depends on coordinated genetic counseling, timely risk-reducing surgery, tailored surveillance, and advanced molecular profiling, with immunotherapy options incorporated when appropriate. Continued research into epigenetic and non-coding RNA biomarkers, along with equitable access to multigene panels, may further refine prevention and treatment strategies for individuals at increased risk.

Management of Other Organ Involvement and Syndromic Variants

Multi-Organ Risk Landscape: Hereditary cancer syndromes extend well beyond breast and ovarian malignancies. Risk estimates, syndromic associations, and other cancer risks for relevant genes are summarized in Table 1 (95% CI, HR/OR as appropriate).[17] Variants in *BRCA2*, *ATM, CHEK2, PALB2*, and *CDKN2A* significantly elevate the risk of developing prostate, pancreatic, gastric, melanoma, and other solid tumors. These cancers are not only more likely to occur at an earlier age but also tend to display more aggressive histologies, highlighting the urgent need for awareness and proactive screening in individuals with these genetic variants.[12,37] Prostate cancer is particularly significant for *BRCA2* carriers, with lifetime risk estimates ranging from 15% to 60%.[38] supported by guideline-based estimates (HR 2.6–4.5; 95% CI varies across cohorts; EMQN).[17] and a higher likelihood of high-grade, early-onset disease. PSA testing and digital rectal exam (DRE) are recommended starting at ages 40–45, tailored to genotype and family history.[16,73] Pancreatic cancer risk also increases among *ATM, PALB2*, and *BRCA* carriers, with synthetic lethality–based agents such as DNA-PKc and ATR inhibitors offering promising therapeutic avenues.[50] Other malignancies—including gastric, melanoma, lung, and mesothelioma—have demonstrated variable links to these genes.[74,75]

Lynch Syndrome and Gynecologic Implications: Lynch Syndrome (LS) is the most common hereditary colorectal and endometrial cancer syndrome, driven by *MLH1, MSH2, MSH6*, and *PMS2* variants. Lifetime endometrial cancer risk can range from 33% to 61%, depending on the gene subtype.[46] Colonoscopy starting at age 20–25, repeated every 1–2 years, is central to mitigating colorectal cancer risk.[47] Risk-reducing hysterectomy with or without RRSO may be recommended for women with high-risk profiles.[16,34] MSI-H/MMR-D status strongly predicts immunotherapy responsiveness, with clear cell ovarian and carcinosarcoma subtypes harboring *POLE* mutations demonstrating durable responses to checkpoint blockade.[44,72]

Genetic Counseling and Founder Patterns: Comprehensive genetic counseling remains critical, especially in complex cases like multiple interacting germline variants (MINAS) or mosaicism, which add uncertainty to individual risk estimates.[76] Founder mutations and family clustering can significantly shape local panel design; for instance, PMS2 exon deletions identified in Qatar and RAD51D variants in certain families illustrate how regional founder effects shape screening pathways.[49,58] For LS, surveillance often includes TVUS, endometrial biopsy, and CA-125 measurements, though their mortality benefit is debated.[46] Emerging epigenetic and non-coding RNA markers—such as *RASSF1A* and *CYB5R4* hypermethylation or the miR-1260 family—could refine risk prediction and enable earlier detection.[24,51,52,54,62,63]

Therapeutic Stratification and Molecular Profiling: Emerging treatment strategies increasingly integrate HRD status, MSI-H/MMR-D classification, and TME features to guide the selection of PARPi or immunotherapy pathways. Recent evidence demonstrates that HRD-positive tumors with high SV burden exhibit upregulated PD-L1 expression, supporting the synergy of checkpoint blockade.[9] Kumar et al.[41] further showed how PARP inhibition can activate the cGAS–STING pathway, enhancing tumor immunogenicity.[41] Molecular profiling now routinely combines PRS, SV mapping, and BRCAness features to strengthen individualized treatment pathways.[9,10,23,37] Major guidelines (ESMO, EMQN, ASCO) emphasize integrating comprehensive panel results, functional reclassification, and population-specific founder data within a multidisciplinary context. Real-world tools and digital workflows continue to support patient engagement and adherence to long-term management.[67,77]

Overall, effective management of multi-organ hereditary cancer risks requires a syndromic approach that aligns gene-specific screening, appropriate risk-reducing surgeries, tailored surveillance, and personalized therapies — including immunotherapy or synthetic lethality-based regimens where indicated. Equitable access, robust psychosocial support, and culturally adapted testing panels remain essential for translating advances in precision oncology into meaningful survival benefits for diverse patient populations.

PSYCHOSOCIAL, FAMILY, AND EQUITY PERSPECTIVES IN HEREDITARY CANCER MANAGEMENT

The ethical and psychosocial landscape of HBOPC management extends far beyond genetic risk calculation — it significantly shapes patient well-being, family dynamics, and equitable access to care. As multigene panels, functional reclassification, and biomarker testing continue to expand, the emotional, social, and systemic factors to consider become increasingly complex. These factors must be carefully addressed to deliver genuinely patient-centered precision oncology.

Psychological Burden and Stigma

Genetic testing can increase distress through uncertainty, fear, and perceived social stigma. Studies report that up to 66% of hereditary cancer syndrome carriers experience anxiety or depression related to their test results, with VUS findings causing particular worry and decisional paralysis.[26,78] Felt stigma — including fears of insurance or employment discrimination — often discourages disclosure of results, especially in regions lacking robust protective laws.[28] The fear of stigma, particularly concerns about discrimination in insurance or job opportunities, frequently leads individuals to avoid disclosing their results. This is especially prevalent in regions that lack strong legal protections. It's crucial to address these issues to encourage openness and support for those affected. Protective factors like optimism, strong social support networks, and tailored decision-support tools such as RealRisks or Tailored Counseling and Navigation (TCN) interventions have been shown to buffer emotional harm and reduce threat perception.[67,79]

Family Communication, Reproductive Choices, and Informed Consent

Cascade testing transforms genetic risk from an individual concern to a family-wide responsibility. Yet,

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many probands struggle to communicate risk: Up to 20% decline cascade outreach or withhold information from relatives.[38,80,81] Cultural norms, gender dynamics, and fear of blame or stigma further complicate these conversations.[28,82] Male carriers may especially underestimate their own risk, lowering uptake among sons or brothers. Reproductive planning adds another deeply personal layer. Preimplantation genetic diagnosis (PGD) is increasingly discussed as a means to prevent mutation transmission.[83,84] While direct-to-consumer (DTC) testing for minors remains ethically contentious due to its unclear psychological impact.[85] Clear, written informed consent should address these tensions, empowering patients to make choices aligned with their values while minimizing family conflict.[86,87] Emerging biomarkers and epigenetic data also introduce new communication challenges, as plasma methylation or non-coding RNA results need to be disclosed carefully to avoid undue anxiety in unaffected relatives.[51,62,63]

Counseling Quality, Access Barriers, and Global Inequities

Guidelines from ASCO, ESMO, and EMQN increasingly emphasize comprehensive, culturally sensitive genetic counseling. However, implementation in practice often falls short. Infrastructure and workforce shortages persist in underserved regions, from sub-Saharan Africa to the Caribbean, where limited laboratory capacity, high test costs, and shortages of trained counselors restrict access to timely testing and result interpretation.[39,55] Cost and insurance coverage remain major obstacles in both low- and high-income settings.[43,88] Racial and gender disparities further limit cascade testing uptake; minority groups and male relatives continue to be underrepresented in outreach and follow-up.[38,57,82] Several program-level innovations illustrate how standardized protocols and proactive psychosocial screening can improve care quality — for example, the BRCA Quality Improvement Dissemination Program (BQIDP) and tools like the NCCN Distress Thermometer.[77,78,89] Yet digital interventions, chatbots, and remote counseling must be equitably designed, or they risk excluding communities with limited internet access and/or limited language support.[67,90] Addressing workforce gaps, strengthening counselor training, and embedding psychosocial screening into routine workflows will be essential to align real-world practice with guideline ideals.[57,89] Functional support for interpreting VUS and multi-omic results are equally important to sustain patient trust in precision medicine.[29]

The rapid evolution of hereditary cancer diagnostics must be matched by robust and equitable psychosocial frameworks. This means integrating resilience-building and mental health supports within genetic counseling, ensuring cascade testing remains family-centered yet culturally sensitive, and tackling structural barriers that limit access for vulnerable populations. As international guidelines converge, policy implementation must bridge the gap so that precision oncology's benefits do not come at the cost of hidden psychosocial harms — nor perpetuate disparities in who can truly benefit.

FUTURE DIRECTIONS AND IMPLEMENTATION STRATEGIES

AI-Supported Variant Classification and Polygenic Risk Scores (PRS)

The rapid growth of AI-powered bioinformatics is transforming how VUS are resolved in hereditary cancer syndromes. Guidelines from ASCO, ESMO, and EMQN highlight that the broader adoption of multigene panels demands faster and more inclusive variant classification workflows.[16,17,34] Recent studies demonstrate that machine learning approaches—such as k-nearest neighbors (KNN), decision trees, and integrated scoring algorithms—can predict *BRCA1/BRCA2* negativity with high accuracy, reaching approximately 93%.[18] Tools like Sophia DDM and MutationTaster accelerate functional confirmation, while locally curated population databases —such as those developed for underrepresented populations in the Caribbean, Tanzania, or Turkey—reduce disparities by improving variant interpretation.[19,39,55] Epigenetic factors—including DNA methylation, LOH, and miRNA signatures—are increasingly integrated into these models to refine "BRCAness" features, enhancing predictions for synthetic lethality and targeted therapies.[10,24] PRS further complement monogenic panel testing, with evidence showing that adding PRS significantly improves risk stratification—especially among *BRCA2* carriers.[37] The challenge now is to embed PRS into clinical workflows without widening existing disparities, an area where decision-support tools like RealRisks have shown early promise.[67]

Real-World Data and International Sharing

Large-scale RWD initiatives help bridge the gap between controlled trials and the diverse realities of he-

reditary cancer populations. Biobanks such as the UK Biobank and Estonian Biobank have shown that many mutation carriers lack classical family history triggers, highlighting the need for broader population-based screening.[7,37,91] RWD refines risk models, clarifies VUS reclassification, and illuminates founder mutation patterns across different regions and ethnic groups.[7,21,47] Cross-border data pooling and harmonized variant databases are critical for balanced classification and for reducing false negatives in underrepresented communities.[14,65] Studies such as the Breast Cancer Family Registry (BCFR) demonstrate how integrating methylation and miRNA profiles adds functional nuance to variant interpretation, while microsatellite instability (MSI) testing innovations further enrich multi-omic datasets.[44,62,92] As digital platforms expand, tools like chatbots and risk-notification pilots emphasize that public trust and clear consent remain as critical as advanced informatics pipelines.[61,93] Robust governance frameworks and transparent data-sharing policies will remain key to ensuring that international data harmonization genuinely translates into better risk prediction and fair access in hereditary cancer care.

National-international Guideline Harmonization and Implementation Strategies

Aligning next-generation diagnostics with practical policy frameworks is essential for delivering inclusive hereditary cancer care. Although NCCN, ESMO, NICE, and ASCO share core principles, practical implementation must reflect local genomic diversity and health system capacity.[16,17,34] Studies show that rigid pedigree-only criteria often miss high-risk individuals; dynamic updates that integrate PRS, regional variant frequencies, and founder mutation data are increasingly needed to close these gaps.[21,37] Policy frameworks should systematically address gender- and culture-related disparities in testing uptake, invest in counselor training pipelines, and fund functional VUS reclassification initiatives.[14,87] The integration of non-invasive biomarkers—such as methylation or miRNA signatures—into early detection guidelines will require rigorous clinical validation and sustainable reimbursement structures to ensure broad access.[24,25,51,52,62,63,71] Practical examples, including Sweden's direct risk-notification model and NCCN-based quality improvement programs, illustrate scalable pathways that can align precision tools with population-specific needs while sustaining public trust and cost-effectiveness.[77,93]

In summary, the next decade of hereditary cancer prevention and care will depend on aligning advanced bioinformatics, robust real-world data integration, and culturally adapted policy frameworks. Doing so promises to shrink diagnostic gaps, personalize risk prediction, and transform precision oncology's potential into measurable survival gains for diverse populations.

Limitations

Most of the evidence synthesized in this review is derived from studies conducted in high-income countries, where access to multigene testing, infrastructure, and trained consultants is more readily available. This geographic concentration of data introduces an inherent bias, as the epidemiology, variant spectrum, and implementation challenges in low- and middle-income countries (LMICs) remain underexplored. Although important contributions have emerged from underrepresented regions—such as reports from the Caribbean and Tanzania—these studies are still relatively few in number and often limited in sample size. Consequently, risk estimates, variant classification rates, and psychosocial outcomes summarized here may not fully capture the realities of health systems with constrained resources. Differences in insurance coverage, cultural norms, and workforce capacity further limit the generalizability of current recommendations. Addressing this imbalance will require not only more region-specific research but also coordinated support from global organizations. In this context, initiatives supported by WHO, IARC, UNDP, and international or private foundations can play an important role in bridging resource gaps, enabling more inclusive testing and counseling programs in LMICs.

CONCLUSION

HBOPC management has progressed into a truly multidisciplinary, multi-omic, and real-world data–driven field that integrates advanced genomic testing, refined variant classification, and nuanced psychosocial frameworks. While *BRCA1/BRCA2* remain the cornerstone, the expanding role of non-*BRCA* genes, region-specific founder mutations, and PRS demands culturally sensitive counseling and adaptable testing strategies.

As illustrated in the Figure 1, future pathways hinge on robust multigene panels, AI-supported reclassification, and the promise of epigenetic and miRNA biomarkers—yet these innovations must be validated and implemented with equitable access in mind.

Table 1 Summary of selected high- and moderate-penetrance genes associated with hereditary breast, ovarian, pancreas and prostate cancer (HBOPC), including founder mutations, estimated lifetime risks for breast and ovarian cancers, other notable cancer risks, syndromic associations, and key management considerations

Gene	Estimated lifetime risk (%)	Other cancer risks (%)	Founder mutations	Syndromic association	Management highlights	Ref.
BRCA1	Breast ~60–72% (HR, 95% CI: 65–79), Ovarian ~39–58% (HR, 95% CI: 36–53), Contralateral breast ~38% at 20 years (HR, 95% CI: 31–45)	Pancreatic ~2–5% (OR 2.58; 95% CI: 1.54–4.05), Prostate ~7–26% (males) (HR 2.5; 95% CI: 1.9–3.3), Male breast ~1% (RR 4.30; 95% CI: 1.09–16.96)	Ashkenazi (185delAG, 5382insC, 6174delT)	Fanconi (biallelic)	MRI 25–29; RRSO ~35–40; PARPi if HRD+	[17,36,94]
BRCA2	Breast ~55–69% (HR, 95% CI: 61–77), Ovarian ~11–25% (HR, 95% CI: 13–29)	Prostate ~19–61% (males) (HR, 95% CI: 19–61), Pancreatic ~5–10% (OR 6.20; 95% CI: 3.5–11.0), Male breast ~1–7%; (RR 83; 95% CI: 44–158), Melanoma	Ashkenazi (6174delT), Icelandic (999del5)	Fanconi (*FANCD1*) if biallelic	MRI 25–29; RRSO ~40–45; PSA from 40 (males)	[17,36,94]
TP53	Breast >60% (OR 5.05; 95% CI: 2.41–10.58), Contralateral ~18–49% (10 yrs)	Sarcoma, CNS, ACC, melanoma; total ~90% risk by 60	Brazilian R337H	Li-Fraumeni Syndrome	Whole-body MRI; avoid RT; organ-specific surveillance	[17,95]
PALB2	Breast ~32–53% (RR 7.18; 95% CI: 5.82–8.85), Contralateral ~5–8% (10 yrs); Ovarian ~3–5% (RR 2.91; 95% CI: 1.40–6.04; SRR 3.08; 95% CI: 1.93–4.67), Male breast ~0.9–1% (to 70–80y) (RR 7.34; 95% CI: 1.28–42.18; OR 6.60; 95% CI: 1.70–21.10)	Pancreatic ~2–3% (to 80y) (RR 2.37–3.34; 95% CI up to 2.21–5.06; OR 7.69; 95% CI: 3.88–14.44)	No major founder; recurrent variants in EU/Asia	Fanconi (*FANCN*) if biallelic	MRI ~30–35; RRSO individualized; MRCP/EUS if FH+	[17,94, 96,97]
PTEN	Breast ~40–60% (OR 5.40; 95% CI: 3.15–9.23)	Thyroid ~20% (absolute risk), Endometrial ~20% (absolute risk), Renal, colorectal, GI hamartomas	No major founder; mosaicism possible	Cowden Syndrome (PHTS)	MRI/mammo ~30–35; thyroid US; endometrial if symptomatic	[17,98]
CDH1	Breast (lobular) ~37–55% (OR 2.66; 95% CI: 1.68–4.20), Ovarian not significant	Diffuse gastric ~35–45% (strong evidence), cleft lip/palate in some families	No major founder; recurrent in specific populations	HDGC; lobular breast carcinoma	MRI/mammo ~30+; consider RRM; prophylactic gastrectomy 20–30	[17,99]
STK11	Breast ~32–54% (OR 1.10; 95% CI: 0.32–3.80), Non-epithelial ovarian ~10–21%	Pancreatic ~10–30%; Colorectal, gastric, small intestine, cervical, lung	No major founder; genotype-phenotype correlations described	Peutz-Jeghers Syndrome (PJS)	MRI/mammo ~25–30; GI endoscopy 2–3 yrs; polyp management	[17,100]
ATM	Breast ~17–52% (up to ~60% for c.7271T>G) (RR 2.10; 95% CI: 1.71–2.57; HR 3.76; 95% CI: 2.76–5.21) Ovarian minimal	Pancreatic ~5–10% (OR 4.21; 95% CI: 1.88–9.47) Prostate/colorectal limited	c.7271T>G in EU cohorts	Ataxia-Telangiectasia (biallelic)	Mammo ~40; MRI ~30–35 if high-risk; RT not contraindicated	[17,94, 101]
BARD1	Breast ~7–25% (up to 20–40% in some cohorts) (OR 2.33; 95% CI: 1.83–2.97; TNBC OR 4.35–11.27)	Limited or no evidence	No major founder; some EU recurrent variants	None recognized	Mammo ~40; MRI if FH+	[17,94]
BRIP1	Ovarian ~5–15% (RR 11.22; 95% CI: 3.22–34.10; OR 20.97; 95% CI: 12.02–36.57; OR 8.13; 95% CI: 4.74–13.95), Breast limited	None clear	No major founder; recurrent variants noted	None recognized	RRSO ~45–50; breast surveillance if FH+	[17,94, 102]
CHEK2	Breast ~20–44% (OR 2.47; 95% CI: 2.02–3.05; OR 2.54; 95% CI: 2.21–2.91; lifetime risk ~24% by 80y), Ovarian minimal	Prostate emerging; colorectal possible	c.1100delC (N. Europe), c.444+1G>A (Polish)	None recognized	Mammo ~40; MRI if high-risk; PSA from 40 (males)	[17,94, 103]
NF1	Breast ~17–28% (<50 yrs) (RR 6.5; 95% CI: 2.6–13.5; RR 4.4; 95% CI: 2.5–7.0; SIR 3.5; 95% CI: 1.9–5.9)	MPNST, GIST, optic glioma, other NF1-related tumors	No major founder	Neurofibromatosis type 1 (NF1)	Mammo/MRI ~30–35; refer to NF1 surveillance	[17,104]
RAD51C	Breast ~15–25% (RR 1.99; %95 GA: 1.39–2.85; age 80 cumulative ≈21% [15–29]), Ovarian ~10–15% (RR 7.55; %95 GA: 5.60–10.19; OR 5.59; %95 GA: 4.42–7.07; age 80 cumulative ≈11% [6–21])	None clear	No major founder; some recurrent	Fanconi (biallelic) rare	MRI/mammo ~30–35; RRSO ~45–50	[17,94]
RAD51D	Breast ~15–20% (RR ~1.8–2.0; 95% CI: 1.1–3.0), Ovarian ~10–20% (RR 7.6; 95% CI: 5.5–10.4; OR 6.6; 95% CI: 4.4–9.8; lifetime risk ≈13% [7–23])	None consistent	No major founder	None recognized	MRI/mammo ~30–35; RRSO ~45–50	[17,94]
MMR Genes	Breast <5%; Ovarian: MSH2/EPCAM ~8–20% (HR 7.5; 95% CI: 4.7–12.0), MLH1 ~4–20% (HR 5.6; 95% CI: 2.9–10.9), MSH6 ~1–13% (HR 2.1; 95% CI: 1.1–4.1), PMS2 ~1–3% (limited evidence; wide CI)	CRC/endometrial very high; pancreas ~5–10% (increased risk, but gene-specific variation) upper GI/urinary tract	Some founders in MSH2 (Ashkenazi); EPCAM large deletions	Lynch Syndrome; CMMRD if biallelic	RRSO for MSH2/EPCAM; CRC scope 1–2 yrs from ~20; endometrial biopsy if indicated	[16,17, 105]

Table 1 (cont.) Summary of selected high- and moderate-penetrance genes associated with hereditary breast, ovarian, pancreas and prostate cancer (HBOPC), including founder mutations, estimated lifetime risks for breast and ovarian cancers, other notable cancer risks, syndromic associations, and key management considerations

Notes:

- All estimates are synthesized from large cohort studies and meta-analyses (e.g., Kuchenbaecker et al., 2017 [36]; Dorling et al., 2021 [94]; Hu et al., 2021 [97]), European Molecular Quality Network (EMQN) Best Practice Recommendations 2024 [17], and relevant ESMO [16] (European Society for Medical Oncology)/ASCO (American Society of Clinical Oncology) updates where applicable.
- Genes are grouped together for practical clinical interpretation, as penetrance levels may vary by population, variant type, and family history.
- Subtype-specific findings (e.g., TNBC prevalence in BRCA1 carriers, ER+ enrichment in BRCA2 carriers) are reported in the main text and may diverge from the standardized guideline ranges shown here, reflecting cohort- or tumor-specific variability.

HDR/DSBR: Homologous DNA repair / Double-strand break repair; RRM: Risk-reducing mastectomy; RRSO: Risk-reducing salpingo-oophorectomy; RT: Radiotherapy; FH+: Positive family history; CMMRD: Constitutional mismatch repair deficiency; MRI: Magnetic Resonance Imaging; Mammo: Mammography; CRC scope: Colorectal cancer screening; HR: Hazard Ratio; OR: Odds Ratio; RR: Relative Risk; CI: Confidence Interval; SIR: Standardized Incidence Ratio; SRR: Standardized Relative Risk; TNBC: Triple-Negative Breast Cancer; ACC: Adrenocortical Carcinoma; CNS: Central Nervous System; GI: Gastrointestinal; GIST: Gastrointestinal Stromal Tumor; MPNST: Malignant Peripheral Nerve Sheath Tumor.

To translate such advances, risk-reducing surgeries, tailored surveillance, and cascade testing should be embedded within supportive ethical and psychosocial infrastructures. Cross-border data sharing, inclusive variant databases, and harmonized global guidelines remain essential to bridge gaps between research and daily practice.

However, the translation of these advances into routine clinical practice continues to be challenged by high costs, limited infrastructure, and the shortage of trained genetic consultants—factors that must be addressed in parallel with scientific progress to ensure sustainable and equitable implementation.

Ultimately, the full impact of this evolving HBOPC paradigm will only be realized when every at-risk family benefits equally from precision medicine, as our multidimensional approach underscores.

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