Hereditary ovarian and breast cancer: what have we learned?

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An autosomal-dominant inherited trait predisposing women to both breast cancer (BC) and ovarian cancer (OC) was first described in 1971. Subsequent strides were made in identifying mutations in the eventually cloned genes BRCA1 and BRCA2 as being responsible for hereditary BC and OC (HBOC) in many women with early-onset HBOC. More recently, modifiers of BC risk have also been identified and are under study. The biological and molecular genetic pathways for malignant transformation in OC (ovarian epithelium and/or epithelium of the fallopian tube or, possibly, the endometrium and endocervix) remain elusive. The answer to the question ‘What have we learned?’ which is part of our chapter title unfortunately remains incomplete. However, intensive worldwide research indicates that its malignant transformation is the product of a multi-step process where there is an array of mutations which account for three or more classes of genes, inclusive of proto-oncogenes, tumor suppressor genes and mutator genes. This causal uncertainty heralds an enormous clinical-pathology dilemma, given the fact that epithelial OC, together with related Müllerian duct carcinoma, harbor the highest fatality rates of all gynecologic malignancies.

**Key words:** BRCA1, BRCA2, Lynch syndrome, family history, duty-to-warn

**introduction**

Ovarian cancer (OC) accounts for ∼225 000 cases each year worldwide, causing over 140 000 deaths [1], while in the United States there are ∼22 280 new OC cases annually and 15 500 deaths [2]. Approximately 90% of cancers believed to have arisen in the ovaries are carcinomas; the remaining primary ovarian malignancies are of either stromal or germ cell origin [3, 4].

Emerging evidence indicates that so-called ‘ovarian’ carcinomas arise either *de novo* through malignant transformation of the ovarian epithelium and/or epithelium of the fallopian tube and perhaps endometrium and endocervix [3, 5, 6]. The biological mechanism for this transformation remains elusive, but it likely involves a multi-step process with mutations accumulating for at least three classes of genes: proto-oncogenes, tumor suppressor genes and mutator genes [7].

Epithelial ‘ovarian’ cancer (EOC), together with related Müllerian duct carcinomas, carries the highest fatality rates of all gynecologic malignancies [8–10]. The majority of patients registered with EOC are diagnosed in advanced stages, and because of the limited efficacy of available therapy in such cases, primary and secondary prevention strategies are critical to reduction of both cancer incidence and mortality. The development of effective prevention methods depends on the identification of the anatomic origins of the disease as well as specific molecular-based carcinogenic mechanisms [5–7].

Inherited susceptibilities to EOC are estimated to account for some 5%–15% of this disease. The hereditary breast-OC (HBOC) syndrome, with mutations in the breast cancer (BC)-associated genes *BRCA1* and *BRCA2*, accounts for some 65–85% of all hereditary EOCs; Lynch syndrome (LS), with mutations in mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), accounts for another 10–15% [7].

Comprehensive family cancer histories are essential to recognize inheritance patterns in family pedigrees, so that clinicians and genetic counselors can provide education and counseling to probands and their families regarding cancer risk status and genetic testing. Management strategies for hereditary cancer syndromes are designed to benefit the family and, in turn, inform them of the legal protection from insurance/employment discrimination through the Genetic Information Nondiscrimination Act. Many of these cancers may be prevented, most confidently through a prophylactic surgery [11, 12].

Current epidemiological, clinical and pathological investigations, coupled with the search for molecular pathways in sporadic and hereditary ovarian carcinogenesis, are basic for prophylaxis, early detection, treatment and final elimination of these cancers in the future.

**epidemiology of hereditary OC**

Ziogas et al. [13] investigated the evidence for cancer among family members of a population-based family registry for BC and OC. This was possibly the first population-based BC and OC family registry and was therefore ideally suited for estimating BC and OC in relatives of BC and OC probands. Their study consisted of reported data from 1567 BC and 328...
OC probands. In their study of non-Hispanic Caucasian BC probands, ‘… relative risk (RR) of breast cancer in mothers and sisters is significantly elevated [RR = 1.7 and 95% confidence interval (CI) = 1.4–2.0 and RR = 2.8 and 95% CI = 2.3–3.3, respectively]. In families of OC probands, mothers were at an increased risk of OC (RR = 4.6; 95% CI, 2.1–8.7). RR of breast cancer in mothers of Hispanic breast cancer probands is significantly elevated (RR = 4.9; 95% CI, 2.6–8.5). No elevation of breast or ovarian cancer risk was observed among relatives of Asian probands.’[13] These findings lend strong support for the need to identify relatives from HBOC families who may be at enormously increased risks for BC and OC and who could be helped through identification before cancer development. Then, they would have an opportunity to undergo DNA testing for BRCA1 or BRCA2 mutations associated with HBOC syndrome, p53 mutations for Li–Fraumeni syndrome, or MMR mutations for LS.

There is considerable evidence for the early onset of hereditary OC. Counseling, screening and/or prophylactic surgery should be offered at earlier ages to BRCA mutation carriers in these families. Soegaard et al. [14] investigated BRCA1 and BRCA2 genes for coding sequence mutations and large genomic rearrangements in 445 confirmed OC cases from Denmark. Special attention was given to the association between OC clinical features and patients’ mutation statuses, and was then extended to cancer risk assessment for first-degree relatives. Findings disclosed pathogenic BRCA1 or BRCA2 mutations in 26 cases (5.8%) of OC patients, with five different mutations identified in more than one individual; this result was consistent with the possibility of an OC founder mutation in Denmark. Mutation carriers were diagnosed at significantly earlier ages than non-carriers (median ages at diagnosis were 49 and 61 years, respectively; \( P = 0.0001 \)). BRCA1 mutations were carried by 23% of women with OC diagnosed before the age of 40 years, 15% of those diagnosed between 40 and 49 years, 4% of those diagnosed between 50 and 59 years and 2% of women diagnosed at ≥60 years of age (\( P = 0.00002 \)). First-degree relatives of mutation carriers had greater relative risks (RRs) for both OC (RR = 10.6, 95% CI = 4.2–26.6; \( P < 0.0001 \)) and BC (RR = 8.7, 95% CI = 3.0–25.0; \( P < 0.0001 \)) when <60 years of age [14].

**History of hereditary ovarian carcinoma and HBOC**

In the early 1970s, Lynch’s group at Creighton University [15–17] provided the first evidence of an autosomal-dominant inherited trait predisposing women to both BC and OC. The first gene linkage evidence of early-onset BC to chromosome 17q21 was given by Hall et al. in 1990 [18]. This first was thought to be site-specific. However, ~1 year later, Narod et al. [19] demonstrated that the same genetic locus was linked to both BC and OC in HBOC syndrome families previously described by Lynch et al. (Figure 1). This gene was termed BRCA1 and was subsequently cloned by Miki et al. [20] A second gene locus at chromosome 13q12.3 [21] was linked to BCs in several additional families, designated as BRCA2 and cloned by Wooster et al. [22, 23] The BC Linkage Consortium [24] subsequently provided data, indicating that some 90% of families afflicted with four or more BCs and even one OC in the linear pedigree were linked to either BRCA1 or BRCA2.

**Importance of family history in OC patients**

vanAltena et al. [25] evaluated family histories obtained in EOC patients with the objective of identifying factors that determine their adequacy. They were assessed for validity by comparison with self-administered questionnaires. Medical records were then reviewed from all 1112 EOC patients registered by the nationwide cancer registry and diagnosed in 11 Dutch hospitals between 1996 and 2006. An adequate family history was defined as ‘… a written notification of the presence or absence of relatives with breast or ovarian cancer. Factors that were correlated with family history taking were identified among univariable and multivariable logistic regression …’ Results showed that of 147 patients who returned a mailed questionnaire, an adequate family history was taken in only 41% of the cases. Detailed hospital work-ups, including those who underwent surgery and/or chemotherapy, were compared with self-administered questionnaires. Disagreement was found in 64% of the cases, mainly resulting from missing data in the medical records. This included documentation of family history being either absent or inadequate in the medical records, a problem that unfortunately appeared in the majority of EOC patients. Clearly, these findings reflect the urgent need for better assessment of hereditary cancer risk, which in our own extensive experience is a problem when interrogating patients for their family histories and attempting to obtain documentation through their medical records. This matter is an urgent one, since such documentation is mandatory, given the advantages of molecular genetics for the ultimate diagnosis of hereditary cancer in families through appropriate DNA testing.

Brozek et al. [26] indicated that, given the estimate that 5–10% of OC patients and 2–5% of all BC patients harbor a BRCA1 or BRCA2 mutation, the majority of families harboring BRCA1 or BRCA2 germline mutations are qualified for molecular testing based upon their family histories of excess of BC or OC. This study was focused on the need for establishing the frequency of positive family histories for cancer in Polish BC and OC patients with or without BRCA1 germline mutations. Brozek et al. analyzed their patients for the presence of four of the most common BRCA1 mutations in Poland, specifically 5382insC (c.5266dupC), 300T>G (P.181T>G), 185delAG (c.68_69delAG) and 3819del5 (c.3700_3704del5). Because of founder effects, these four mutations comprise 70–90% of all BRCA1 pathogenic mutations in the Polish population. Their investigation involved a patient group consisting of ‘… 1845 consecutive female breast and 363 ovarian cancer cases. 19 out of 37 (51%) of BRCA1-positive ovarian cancer patients and 21 out of 55 (39%) BRCA1-positive breast cancer [patients] had negative family history of breast and/or ovarian cancer among first- and second-degree relatives. In ovarian cancer patients, negative family history was more frequent in those with 300T > G BRCA1 gene mutation than in 5382insC carriers. This finding indicates the necessity of searching for 300T > G mutation in families with a single diagnosis of ovarian cancer in [the] family …’ These findings of a high frequency of mutations
detected in BC patients lacking family histories showed that ‘… breast cancer patients should be qualified for genetic testing on the basis of wide clinical and pathological criteria.’ Clearly, there will be a pick-up of OC based upon the high frequency of its association with BC in the HBOC syndrome.

LS
In the 1960’s, Lynch et al. [27, 28] defined a familial syndrome showing autosomal-dominant transmission of susceptibility to colorectal cancer (CRC) with predilection proximal to the splenic flexure occurring in younger than expected adults (mean age ∼45 years) but with no excess of adenomatous colonic polyps. Increasingly, publications on the syndrome made it evident that members of these kindreds were prone to excesses of primary synchronous and metachronous CRCs in addition to extracolonic cancers including carcinomas of the endometrium, ovary, stomach, small bowel, hepatobiliary tract, pancreas, renal pelvis, ureter, breast, prostate and brain tumors (particularly glioblastomas) [29–33]. Relevant to female members of LS families, the cumulative lifetime risk (to age 70 years) for primary endometrial cancer was found to be greater than their risk for CRC [34–36]. In several studies, the lifetime risk and standardized incidence ratios for primary OC, compared with population risk, exceeded that of all other primary extracolonic malignancies other than endometrial cancer in the women.

molecular genetic revolution: exomes and next-generation sequencing
We are in the midst of a sea change in how we interpret the multiple phenotypic and genotypic characteristics of hereditary cancer, which is attributable in a major way to the ongoing molecular genetic revolution and its impact on cancer diagnosis, surveillance and management. Newly developed ‘next-generation’ DNA sequencing (NGS) technologies provide remarkable power for the genome study with relatively low cost, simple sample preparation, high speed, mass production and the ability to sequence individual and population genomes. For example, exome sequencing analyzes only the protein-coding region (exon) of the genome, which contributes ∼85% of genetic disease-causing mutations [37]. Costs are substantially less than sequencing the whole genome, and analyzing exon sequences is simpler than analysis of the whole genome. Information identified in affected genes then can be biologically translated [37–41].

hereditary BC: genotypic heterogeneity
Approximately 20–25% of BC cases are familial. However, in spite of mounting evidence of the impact of BC familial clustering, progress has been slow in identifying its genetic predisposition. Some of this delay has been related to the phenotypic and genotypic heterogeneity of familial BC, including patterns of multiple primary cancers such as the HBOC syndrome, caused by mutations in BRCA1 and BRCA2, with its pattern of excess BC and OC; the Li–Fraumeni syndrome, caused by mutations in the p53 gene, with an excess of BC, sarcomas, brain, adrenocortical and multiple other cancers; PTEN mutations that cause an excess of breast, colon, thyroid and other cancers; and the MMR gene mutations that cause LS with its predilection to CRC, endometrial, ovarian and other extracolonic cancers.

Besides these high-risk mutations, intermediate-risk mutations include CHEK21100delC associated with an increased risk of BC and CRC, as well as BC-predisposing mutations in ATM, BRIPI, and PALB2. More recently, very modest-risk genetic variants have been identified, such as single nucleotide polymorphism (SNP) detected by genome-wide association studies (GWAS) in or close to FGFR2, TNRC9, MAP3K1 and LSP1.

The ‘high-risk’ BC susceptibility genes account for only 20–25% of all familial BC risk. Adding known ‘intermediate-risk’ genes does not increase this by more than a few percentage points. Finally, 20 very common ‘modest risk’ gene variants are known, but together these account for <10% of observed familial risk.

gene modifiers in HBOC
Rebbeck et al. [42] recently identified genes that encode proteins which interact with BRCA1 as modifiers of BRCA1-associated BC. This investigation involved a comprehensive set of genes that encode most BRCA1 interactors in order to evaluate the role

Figure 1. Pedigree of original family demonstrating the linkage of both breast (BC) and ovarian cancers (OC) to BRCA1.
of these genes as cancer-risk modifiers. They studied a cohort of 2825 BRCA1 mutation carriers for association of BC and OC diagnoses with haplotypes at ATM, BRCC36, BRCC45 (BRE), BRIP1 (BACH1/FANCJ), CTIP, ABRA1 (FAM175A), MERIT40, MRE11A, NBS1, PALB2 (FANCN), RAD50, RAD51, RAP80 and TOPBP1. These investigators observed ‘… Statistically significant false discovery rate (FDR) adjusted P values for overall association of haplotypes (P_FDR) with breast cancer were identified at ATM (P_FDR = 0.029, BRCC45 (P_FDR = 0.019), BRIP1 (P_FDR = 0.008), CTIP (P_FDR = 0.017), MERIT40 (P_FDR = 0.019), NBS1 (P_FDR = 0.003), RAD50 (P_FDR = 0.014), and TOPBP1 (P_FDR = 0.011). Haplotypes at ABRA1 (P_FDR = 0.007), BRCC45 (P_FDR = 0.016 and P_FDR = 0.005 in two haplotype blocks), and RAP80 (P_FDR < 0.001) were associated with ovarian cancer risk …’ They concluded that their data suggested the presence of genomic variation ‘… at multiple loci that encode proteins that interact biologically with BRCA1 are associated with modified breast cancer and ovarian cancer risk in women who carry BRCA1 mutations’. In another study, Rebbeck et al. [43] looked at a cohort of 1575 BRCA1 and 856 BRCA2 mutation carriers in order to ‘… evaluate haplotypes at ATM, BRAD1, BRIP1, CTIP, MRE11, NBS1, RAD50, RAD51, and TOPBP1 in ovarian cancer risk. In BRCA1 carriers, no associations were observed with ATM, BRAD1, CTIP, RAD50, RAD51, or TOPBP1. At BRIP1, an association was observed for one haplotype with a multiple testing corrected P (P_corr) = 0.012, although no individual haplotype was significant. At MRE11, statistically significant associations were observed for one haplotype (P_corr = 0.007). At NBS1, we observed a P_corr = 0.024 for haplotypes. In BRCA2 carriers, no associations were observed with CTIP, NBS1, RAD50, or TOPBP1. Rare haplotypes at ATM (P_corr = 0.044) and BRAD1 (P_corr = 0.012) were associated with ovarian cancer risk. At BRIP1, two common haplotypes were significantly associated with ovarian cancer risk (P_corr = 0.011). At MRE11, we observed a significant haplotype association (P_corr = 0.012), and at RAD51, one common haplotype was significantly associated with ovarian cancer risk (P_corr = 0.026’.

Thus, it may be that OC risks are influenced by variable penetrance among mutation carriers [42], associated with variations in genes that encode for proteins which interact with BRCA1 and BRCA2 in such a way to affect OC risk. Such genes include ATM, BRAD1, BRIP1, MRE11A and RAD51 [43].

RAD51D germline mutations and susceptibility to OC
Recent GWAS findings identified a locus on chromosome 19p13 as a modifier of BC risk for BRCA1 mutation carriers [44], and a RAD51 SNP was found to modify OC risk for BRCA2 mutation carriers [45].

Meindl et al. identified families with HBOC who manifested RAD51C [46]. This finding prompted Loveday et al. [47] to study the role of RAD51D in cancer susceptibility and therein they identified eight inactivating RAD51 mutations in unrelated individuals from 911 HBOC families compared with one inactivating mutation being identified in 1060 controls (P = 0.011) [47]. The association was found primarily for OC, with three mutations identified in the 59 pedigrees that contained at least three individuals with OC (P = 0.0005). The RR of OC for RAD51D mutation carriers was estimated to be 6.30 (95% CI, 2.86–13.85, P = 4.8 × 10⁻⁶). In contrast, the RR of BC was estimated to be 1.32. Meindl et al. concluded that RAD51D mutation testing may have important clinical utility in women affected with OC and their families. They also showed that cells deficient in RAD51D appeared to be sensitive to treatment with PARP inhibitor, thus posing a possible therapeutic approach for cancers arising in RAD51D carriers [47]. Furthermore, genomic variations at multiple loci encoding proteins which biologically interact with BRCA1 were found to be associated with modified BC and OC risk in women harboring BRCA1 mutations [42].

OC cluster region
Gayther et al. [48, 49] identified truncating mutations clustered in a BRCA2 region of ~3.3 kb in exon 11 in families with the highest proportionate risk of OC compared with BC (P = 0.0004). Based on a subsequent study by Lubinski et al. [50], this was attributable to both the relatively high risk of OC and the relatively low risk of BC. The Lubinski et al. study included 440 families with 140 distinct BRCA2 mutations which supported the assignment of the OC cluster region to that which is spanned by nucleotides 3035 and 6629. Families with mutations located within this region were approximately twice as likely to contain women affected with OC as were families carrying other mutations (OR = 2.21; P = 0.0002). Thompson et al. [51, 52] reported higher ratios of OC to BC in the central regions of BRCA1 and BRCA2 and confirmed reduced risk of OC with 3 mutations of BRCA1. Lubinski et al. [50] concluded that their study provided ‘… compelling evidence that the risk of ovarian cancer in all BRCA2 families is not uniform …’ Lynch et al. [7] later discussed the possibility that ethnic background coupled with the position of the mutation may contribute to phenotypic variations observed in families with BRCA2 mutations.

screening and management
screening for OC
Identification and management of families at increased risk for OC have major public health implications. Considering the inefficiency of screening for OC, the US Preventive Services Task Force (USPSTF) [53] has reaffirmed its 2004 recommendation against screening asymptomatic women. Though the USPSTF recommendation against OC screening excludes women with known genetic mutations who bear increased risk, prophylactic bilateral salpingo-oophorectomy carried out by age 35–40 years is a more efficient alternative for prevention of advanced stage OC [54].

OC risk reduction
Based on their calculated incidence rates, Finch et al. [55] estimated the risk of OC to be 62% for BRCA1 mutation carriers and 18% for BRCA2 mutation carriers in women up to age 75 years with both ovaries intact. The estimated risk of OC following BC was ~13% at 10 years for BRCA1 mutation carriers and 7% at 10 years for BRCA2 mutation carriers, while the level of OC risk
reduction associated with prophylactic salpingo-oophorectomy was estimated to be as high as 95% [55].

Prophylactic salpingo-oophorectomy, particularly if done before menopause, also provides significant protection against BC. A study by Kauff et al. [56] demonstrated 72% reduction of BC in BRCA1 mutation carriers, but only a nonsignificant reduction of BC in BRCA2 mutation carriers who had undergone salpingo-oophorectomy. However, a study by Eisen et al. [57] determined a 56% risk reduction of BC in BRCA1 mutation carriers and a 46% BC reduction in BRCA2 mutation carriers after salpingo-oophorectomy. A subsequent meta-analysis by Rebeck et al. [58] confirmed reduction in BC risk for both BRCA1 and BRCA2 mutation carriers, with a hazard ratio (HR) following salpingo-oophorectomy of 0.47 for BRCA1-associated BC, 0.49 for BRCA2-associated BC and 0.49 for combined BRCA1/2-associated BC.

In their study of women who carried germline mutations for LS, Schmeler et al. [12] identified 61 mutation carriers who had undergone hysterectomy with or without bilateral salpingo-oophorectomy. These cases were matched with 210 mutation-positive women who had not undergone those procedures for analysis of endometrial cancer outcomes. They also matched 46 mutation carriers who had had only salpingo-oophorectomy with 223 control subjects who had not for OC outcomes. Patients were followed from the date of surgery until the occurrence of cancer or until the data were censored at the time of the last patient visit. Of keen interest was the absence of endometrial, ovarian or primary peritoneal cancer among those women who had undergone previous surgery. These authors reported that, ‘... Endometrial cancer was diagnosed in 69 women in the control group (33 percent) for an incidence density of 0.045 per woman-year, yielding a prevented fraction (the proportion of potential new cancers prevented) of 100 percent (95 percent confidence interval, 90 to 100 percent). Ovarian cancer was diagnosed in 12 women in the control group (5 percent), for an incidence density of 0.005 per woman-year, yielding a prevented fraction of 100 percent (95 percent confidence interval, −62 to 100 percent).’ Clearly, hysterectomy with bilateral salpingo-oophorectomy was shown to be effective in the prevention of both endometrial cancer and OC in women with LS-associated germline mutations.

Westin et al. [59] surveyed a total of 544 women who were at a high risk for BC and OC; 313 (58%) responses were received from mailed questionnaires. There were two major management options available to them for risk reduction of OC, either periodic screening (PS) or risk-reducing salpingo-oophorectomy (RRSO). Findings disclosed a high overall satisfaction rate among respondents who had chosen RRSO. This study found that, ‘... The median SWD [Satisfaction With Decision] score was significantly higher in the RRSO group compared with the PS group (P < 0.001). BRCA mutation carriers had higher median SWD scores regardless of management type (P = 0.01). Low satisfaction scores were associated with high levels of uncertainty and the perception that the decision between PS and RRSO was difficult to make (P = 0.001). Satisfaction was unrelated to demographics, clinical factors, or concerns of cancer risk...’ The majority of women faced with a high risk for BC and OC were satisfied with their choice of risk-reduction strategy.

**duty to warn**

**proband-mediated contact**

A highly pertinent question from the patient’s perspective is whether a proband has the responsibility of informing relatives about the familial mutation, even if the relatives do not want to know. Is the patient responsible for notifying family members that a parent, sibling or other close relative has HBOC syndrome or LS? What happens if the patient fails to communicate this information to his or her relatives for personal reasons? Should it instead be a responsibility of the physician or perhaps even a government department of health? Can notification be forced and, if so, under what circumstances?

It is important that physicians, genetic counselors, social workers and other key health care workers encourage probands and their key relatives to discuss with other high-risk family members the importance of DNA testing and the natural history of the hereditary cancer syndrome existing in their families. Attention should be given to motivating factors and barriers that may exist related to genetic testing. Relatives should be compassionately educated so that they can more effectively grasp the potential benefit that may be accrued through knowledge and how this can foster effective cancer control measures. Thereby, family members can effectively reinforce the information they receive from their physicians and genetic counselors, hopefully altering the clinical courses of their specific hereditary cancer syndromes.

Reviewing this subject, Aronson [60] noted that the overall uptake for LS testing was lower than anticipated based upon expressed interest [61, 62]. She found that a strong motivator was relief from uncertainty through learning that an at-risk relative was not a mutation carrier [61, 62]. Testing was also possibly motivated by the need for making decisions about family planning and reproductive matters [61].

Aktan-Collan et al. [63] noted that informing relatives of serious genetic conditions segregating in their families may be mentally challenging and disappointing for probands, especially when considering distant relatives. Because of this, probands tend to inform the nuclear family rather than more distant relatives, leaving the latter unaware of their risk status [64]. Probands who fear blame and discrimination from other family members, and/or intensely fear employment or insurance discrimination, might simply refuse to participate in the process. Our own experience indicates that the overwhelming majority of hereditary cancer-prone families identified and managed in a typical clinical setting will involve the proband and perhaps that individual’s first-degree relatives as part of a nuclear family, but rarely more distant potentially at-risk relatives. Those relatives, if not contacted and given sufficiently detailed information about the possibility of high cancer risks in their family and the implications for diagnosis and control, unfortunately may sustain cancer-related morbidity and mortality as a consequence of their failure to be tested and effectively screened and managed [65, 66].

Aktan-Collan et al. [63] studied healthy adult members of LS families, each harboring a 50% risk of carrying a mutation predisposing to LS. Solicitation of 286 individuals by letter resulted in 112 family members who participated in counseling...
and predictive testing. One month after testing, 73 respondents provided baseline information which was then compared with information from 299 subjects who had been approached via the proband in a previous study [67–69]. Their findings showed that, of the 51% who consented to the study, 92% approved of the direct contact. The attitudes of relatives and the psychosocial consequences were encouraging and similar to those using the proband-mediated approach. This study demonstrated the usefulness of direct contact when a life-threatening but treatable hereditary disease, such as LS, is involved. Aktan-Collan et al. [63] noted that the mean age of the contacted family members was appreciably >25 years, the age conventionally recommended for initiating colonoscopy among LS mutation-positive individuals. Therefore, it is not surprising that among the 32 mutation-positive individuals, colorectal neoplasia was identified in 11 (34%) with the first post-test colonoscopy, and that two of these patients manifested locally advanced disease. This study was in part a response to the investigators’ earlier experience involving their predictive genetic testing program, in which some relatives who had not applied for genetic counseling developed colon cancer [67]. Without exception, these individuals expressed disappointment that their relatives

Figure 2. Pedigree of a classical HBOC family with a BRCA2 mutation.
had not warned them of the risks. In addition, the previous program had confirmed high levels of satisfaction and had found no serious psychological side-effects related to testing [67–69]. These results have since been confirmed by other investigations [70–72]. Attitudes may be different when the disorder, such as carcinoma of the pancreas, has a severely dismal outlook because of the inability to detect early and because of the high mortality rate when diagnosed, even under the best of circumstances.

In summary, Aronson [60] emphasized the need for clinicians to be knowledgeable about the multiple complex ethical, legal and psychosocial concerns surrounding genetic testing for hereditary cancers, where the counselor’s role is to explore facts ‘… that are likely to motivate, deter, and cause distress in probands who wish to undergo genetic testing. Exploring these issues, assessing the risk in the family, and relaying the necessary information about the genetic syndrome and testing process, provides the tools to allow the proband to

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**Figure 3.** Pedigree of a complex family with *BRCA* mutations in both paternal and maternal lineages.
make an informed decision about genetic testing and enables the genetic counselor to best facilitate this process\textsuperscript{[60]}. 

**direct contact with family members**

Questions arise as to the physician’s duty to warn individuals of their cancer risk status when a proband declines to inform at-risk relatives of a hereditary disorder carried in their family.

Offit et al. \textsuperscript{[73]} appropriately noted that if physicians were to assume primary responsibility of identifying and counseling family members who might be at inordinately high hereditary cancer risk, he or she may find it impossible to reach all of the at-risk family members. This fact, coupled with the attendant threat of liability for physician involvement, would discourage some physicians, including those involved in the emerging subspecialty of genetic medicine, from undertaking this task. In the United States, federal as well as certain state regulations safeguarding patients’ confidentiality and genetic privacy may be in conflict with court decisions making the physician liable for failure to warn relatives of hereditary disease risks \textsuperscript{[73–75]}.

Several groups have proposed that the duty to warn patients may help waive the requirement for confidentiality in cases of life-threatening diseases that may have prevention and treatment options \textsuperscript{[76–80]}. In a survey of the literature, Aktan-Collan et al. \textsuperscript{[63]} found studies which acknowledged that confidentiality may be breached in the interest of preventing harm under such conditions \textsuperscript{[81]}.

Physicians’ involvement in ethical and legal concerns about ‘failure to warn’ has led to positions being taken by the American Medical Association \textsuperscript{[82]} and the American Society of Clinical Oncology \textsuperscript{[83]}, wherein these organizations have noted that the physician’s obligations (if any) “… to patients’ relatives are best fulfilled by communication of familial risk to the individual undergoing testing. Such communication about familial risks should be carefully documented as part of the process of an informed consent before testing and at time of counseling … Because the laws of Mendel will continue to apply to these new markers of genetic risk, the issues surrounding familial notification will loom even larger. The

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**Figure 4.** Pedigree of a HBOC family with varying ages of ovarian (OC) and breast cancer (BC) onset.
increasing availability of DNA testing will require greater emphasis on informed consent as a process of communication and education, so as to better facilitate the translation of genomic medicine to clinical practice'[73].

Offit et al. [73] commented on failures to warn family members about their hereditary disease risk that have resulted in at least three malpractice suits against physicians in the United States [75, 84, 85]. They stated that conflict may arise concerning physicians' ethical obligations ‘… regarding the conflict between the physician’s ethical obligations to respect the privacy of genetic information versus the potential legal liabilities resulting from the physician’s failure to notify at-risk relatives. In many cases, state and federal statutes that bear on the issue of ‘duty to warn’ of inherited health risk are also in conflict …’ and they concluded that healthcare professionals have a responsibility to warn, ‘… to encourage but not to coerce the sharing of genetic information in families, while respecting the boundaries imposed by the law and by the ethical practice of medicine'[73].

Offit et al. also discussed a Presidential Commission report [86] which defined conditions ‘… under which it would be ethically acceptable for physicians to breach confidentiality and disclose information to relatives. These conditions include (1) the high likelihood of harm if the relative were not warned, (2) the identifyability of the relative, and (3) the notion that the harm resulting from failure to disclose would outweigh the harm resulting from disclosure [86–88]. In the absence of a federally defined legal ‘duty to rescue,’ which exists in certain parts of Canada [89], the health care professional’s duty to warn is generally viewed as discretionary and not compulsory, ie, legally excusable and not legally mandated[73]. Obviously, the conflict between confidentiality and the duty to warn has not been completely resolved.

**genetic counseling**

A new era for genetic counseling has evolved thanks to the cloning of BRCA1 and BRCA2. Before the discovery of BRCA mutations, it was necessary to rely solely on an individual’s family history. Now we can estimate lifetime risks for BC and OC by DNA testing. This enables women to make decisions about screening, prophylactic surgery and chemoprevention strategies. Advantages are that mutation carriers can potentially avoid morbidity and early mortality through prevention. Non-carriers can avoid the economic and emotional stress of a lifetime of preventive activities, and progeny can receive the ‘good news’ that their high-risk parent did not carry the family’s deleterious BRCA germline mutation, thereby assuring that they did not inherit it. Genetic testing now provides a sound basis for management and patient decisions.

**psychosocial limitations**

Because of the implications for morbidity and mortality, risk to progeny and financial costs, psychosocial matters include: (i) concerns about insurance and employment discrimination; (ii) need to keep updated communication with patients; (iii) scapegoating by family members, such as ‘Why did you bring me into the world knowing that our family cancer risk is so high?; (iv) anxiety and drastic lifelong fear of cancer if the patient is found to harbor a cancer-associated mutation; (v) individuals not wanting to know molecular genetic test results (~20% of our patients who have been tested decline to receive this information about their gene status); (vi) patient’s emotional stress surrounding needs to tell loved ones about the family history, including in advance of marriage and (vii) concerns about how patients may cope most effectively with this distress.

**genetic counselors and centers of expertise**

Genetic counseling is time and labor intensive. Busy clinicians may not have the time necessary to provide education about germline mutation testing, the significance of a positive or negative DNA test and the appropriate management alternatives for germline mutation carriers. Utilization of genetic counselors has made a great difference in the availability of this information. Patients may receive life-saving benefit through advice from these highly trained professionals whose commitment is delivering knowledge, guiding DNA testing of consenting and fully informed individuals, and thoroughly discussing the options for screening and prophylaxis to potentially alleviate cancer morbidity and mortality.

It is important that information regarding cancer risk, DNA testing and cancer control implications is made available to all family members in possible lines of inheritance. Resources for
help, such as genetic counseling, medical geneticists, centers of cancer genetic expertise and informed physicians, should be made known to affected families by their medical caregivers and through public information programs. When referrals are made for cancer genetics counseling and care, this should include all key medical, genetic and genealogic findings.

**informative OC pedigrees**

Figure 2 represents a family showing a classical pattern of HBOC, wherein a BRCA2 mutation has been identified. The classical characteristics are depicted by early-onset BC in the proband (IV-3), her mother (III-2) and a maternal cousin (IV-10). In addition, there are two generations of male BC cases (III-6 and IV-12). However, there is only one case of OC, in the proband’s daughter (V-5) at age 49. The OC risk in BRCA2 carriers is ~15–20% when compared with 45%–60% risk for BRCA1 carriers. Therefore, a reduced incidence of OC in BRCA2-positive families is expected when compared with BRCA1-positive families.

Figure 3 shows an example of a family with an extremely complex family history, wherein all the details need to be documented and explored in order to provide each individual with the most comprehensive and accurate risk assessment available. The proband (V-9) presented for genetic counseling requesting cancer risk assessment because of her paternal family history, which is significant for three male BC cases (IV-11, IV-9 and IV-10) and an early-onset female BC in her aunt (IV-12). Genetic testing identified a BRCA2 mutation within the paternal lineage. However, the proband’s maternal lineage became just as significant and worrisome as the pedigree was explored, with identification of four OC cases (IV-2, IV-13, III-1 and III-3). Interestingly, no BC cases were reported but a BRCA1 mutation was identified within the proband’s maternal lineage. It is essential for both sides of a patient’s pedigree to be developed and studied.

Figure 4 depicts an HBOC family with an identified BRCA1 mutation. There are multiple cases of OC (IV-8, IV-9, IV-14, III-4 and II-2) with the ages of onset ranging from 29 to 71 years. Variation in the age of onset is also found in the BC cases which range from age 27 to 71 years. Screening recommendations should be provided based on the mutation as well as the clinical picture presented in the family.

The proband in the family seen in Figure 5 sought genetic testing and counseling because of her personal BC history as well as her family history. She was concerned about her daughters’ risk for BC, but then also learned about the OC risk for herself and other mutation-positive female relatives when a BRCA1 mutation was identified. The proband and her sister opted to undergo prophylactic hysterectomies and bilateral salpingo-oophorectomies together even though there was no evidence of OC in the family at the time. No cancer was found upon pathological review.

Figure 6 depicts a family that demonstrates a strong pattern of OC. It is noteworthy that there are four generations affected with OC, in individuals II-2, III-3, IV-5 and V-5. Some families, such as this one, are easily identified as hereditary, whereas other pedigrees are more subtle.

This family seen in Figure 7 demonstrates a classical pattern of HBOC with four cases of BC and six cases of OC. Individuals II-2 and IV-15 have been tested for BRCA1, BRCA2 and p53 mutations and none have been identified. Developing new testing techniques will hopefully identify the genetic basis for the increased prevalence of BC and OC in this family, so in the future unaffected family members can be provided with more accurate cancer risk assessment and management plans.

Figure 6. Pedigree of a family with a strong history of ovarian cancer (OC) through four generations.
summary
The biological and molecular genetic pathways for malignant transformation in OC (ovarian epithelium and/or epithelium of the fallopian tube or, possibly, the endometrium and endocervix) remain elusive. The answer to the question “What have we learned?” which is part of our chapter title, unfortunately remains incomplete. However, intensive worldwide research indicates that its malignant transformation is the product of a multi-step process where there is an array of mutations which account for three or more classes of genes, inclusive of proto-oncogenes, tumor suppressor genes, and mutator genes. This causal uncertainty heralds an enormous clinical-pathology dilemma, given the fact that epithelial OC, together with related Müllerian duct carcinoma, harbor the highest fatality rates of all gynecologic malignancies.

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