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Review

Cancer genetics in oncology practice

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Summary

Cancer is a genetic disease caused by the progressive accumulation of mutations in critical genes that control cell growth and differentiation. Completion of the Human Genome Project promises to revolutionize the practice of Medicine, especially Oncology care. The tremendous gains in the knowledge of the structure and function of human genes will surely impact the diagnosis, prognosis and treatment of cancer. Moreover, it will lead to more effective cancer control through the use of genetics to quantify individual cancer risks. This article reviews the current status of genetic testing and counseling for cancer risk assessment and will suggest a framework for integrating such counseling into oncology practice.

Key words: *BRCA1*, *BRCA2*, cancer genetics, cancer screening, familial risks, FAP, genetic counseling, HNPCC, prevention

Introduction

Genetic counseling translates basic scientific knowledge into a practical and understandable form of information for the patient. The ethical, legal and psychosocial implications of genetic testing for inherited cancer syndromes are such that adequate counseling pre- and post- genetic testing is mandatory. Many professional groups including the American College of Medical Genetics and the National Society of Genetic Counselors, the American Society of Clinical Oncology and the European Familial Breast Cancer Collaborative Group have published policies and guidelines as well as a curriculum of essential concepts in cancer genetics required of all health professionals [1–5]. These guidelines emphasize the importance of counseling prior to genetic testing for adult onset cancers. While genetic testing has become standard of care for rare conditions such as familial adenomatous polyposis and medullary thyroid carcinoma, testing remains underutilized in oncology practice.

With completion of the Human Genome project, the medical community stands poised to take advantage of the new knowledge. A number of susceptibility genes for common cancers such as breast, ovary and colon have been identified and individuals with family histories of such cancers can have a more precise estimation of their risk through the use of genetic testing (Table 1). This has led to the development of programs offering genetic counseling for cancer with the intent of incorporating genetic testing in the clinical management of cancer patients and their at risk relatives. The American Society of Clinical Oncology encourages use of genetic testing for cancer in the context of a comprehensive cancer risk assessment [3]. Until we have a clear understanding of the risks, benefits and limitations of genetic tests, it is preferable that genetic testing be performed at centers with access to the educational, counseling, research and follow up resources currently available only at major medical centers. Nonetheless, it is imperative that all health care providers, in particular those in oncology practice have a proper understanding of the issues surrounding genetic testing and counseling. Oncologists could play a pivotal role in cancer prevention through their ability to access cancer patients and their at risk family members. The responsibility to accurately assess familial cancer risks, and counsel patients about the appropriateness of more specialized genetic counseling and testing should become an integral part of a comprehensive oncology practice. In North America, Oncologist have been actively engaged in bringing cancer genetics to the clinic; in Europe while there is increasing awareness among Oncologists, genetic counseling is mainly provided in the few specialized onco-genetics clinics available in the different countries [2].

Breast cancer genetics

Breast cancer poses a major health problem for women in most industrialized countries of the world. Epidemiological studies have provided much information on important risk factors for the disease [6, 7]. These include age, family or personal history of breast cancer, reproductive history and exposures to specific carcinogens. In a series of breast cancer patients presenting in an oncology clinic, Lynch et al. documented a family history of breast cancer in 32% of 325 consecutive breast

cancer patients seen in the clinic [8]. However, estimates from population based studies suggest that only 5%–10% of breast cancers are explained by germline mutations in highly penetrant susceptibility genes such as *BRCA1* and *BRCA2* [9, 10]. These mutations are inherited in an autosomal dominant fashion with varying penetrance [11–13]. Young age at diagnosis (< 45 years old), multiple affected members in a family, bilateral disease and association with other cancers, particularly ovarian cancer and sarcoma are features of inherited breast cancer that can aid clinicians in recognizing individuals who may be carriers of mutations in a breast cancer susceptibility gene.

Breast cancer risk assessment

Data from different epidemiological studies have been used to derive a woman's cumulative breast cancer risk. Tabular risk data compiled by Claus et al. from the Cancer and Steroid Hormone Study (CASH) are available and can be readily applied to clinical situations [6]. The CASH data takes into account age of onset of affected relatives, which has been shown to be a strong predictor of hereditary risk. The Gail model uses five variables including: current age, age at first live birth, age at menarche, number of first-degree relatives with breast cancer and number of breast biopsies to calculate risk ratios [14]. A modified Gail model is available for clinical use and can be readily accessed through the US National Cancer Institute website at http://cancernet.nci.nih.gov/bcra_tool.html [15]. Unfortunately, the Gail model may underestimate hereditary breast cancers because it does not consider paternal family history or the presence of breast cancer in second-degree relatives, nor does it take into account cases of ovarian cancer in the family. The Claus model may be more applicable to individuals with inherited breast cancer because it incorporates age of cancer in affected first and second degree relatives. Both models remain clinically useful tools despite their limitations. The modified Gail model is widely used as a tool for risk assessment in the National Surgical Adjuvant Breast and Bowel breast cancer prevention trials [16]. For families with breast cancer, Couch et al. [17], Parmigiani and Berry [18] as well as Frank et al. [11] have published different models for calculating the probability of finding an inherited mutation in *BRCA1* and *BRCA2* genes. These models are readily available and can aid clinicians and genetic counselors in determining who is most likely to benefit from genetic testing.

Breast cancer susceptibility genes

Although mutations in several genes confer increased breast cancer risk, *BRCA1*, *BRCA2* and *TP53* genes appear to be the most relevant in the clinic (Table 1). To date, deleterious mutations in *BRCA1* and *BRCA2* account for the largest proportion of inherited breast cancers. The proportion of inherited breast cancers due to *BRCA1* and *BRCA2* range in estimate from 30% in clinic based families to 84% in the Breast Cancer Linkage Consortium [18–20]. *TP53* and *PTEN* each account for less than 1% of cases [21, 22]. Heterozygous *ATM* mutation carriers have an increased risk of breast cancer but the magnitude of risk is not quantified [23]. Other genetic conditions with associated breast cancer risks include Muir Torre syndrome with *MLH1* mutations and Peutz Jeghers syndrome with *LKB1/STK1* mutations (Table 1). One of the major limitations of genetic testing in the clinical setting is that it now mostly focuses on identifying mutations in *BRCA1* or *BRCA2* genes and may falsely reassure patients with mutations in other cancer susceptibility genes.

BRCA1 gene

In 1990, investigations in families with a high incidence of breast and/or ovarian cancers led to the localization of a single autosomal dominant cancer susceptibility gene called *BRCA1* on chromosome 17q12–21.1 [24]. The gene was cloned in 1994 and is now marketed as a clinical test licensed by Myriad Genetics Laboratories [11, 25]. When there are multiple breast cancers in a family, the frequency of *BRCA1* mutations ranges from 7% (families with only breast cancer) to 40% (families with both breast and ovarian cancer) [17]. Even among women with early onset of breast cancer, *BRCA1* mutation rates vary from only 3.3%–8%, despite the view that early onset is the best predictor of *BRCA1* mutations in the absence of family cancer histories [19].

A recent report examined the contribution of *BRCA1* and *BRCA2* to inherited breast cancer when there were at least four cases of breast cancer diagnosed under age 60 years within a family. These authors found that *BRCA1* was associated with 52% of families and *BRCA2* with 32% of families [20]. Neither gene was associated with breast cancer in 16% of families, consistent with the view that there may be at least one remaining unidentified breast cancer susceptibility gene. Moreover, when both breast and ovarian cancer were present in families from this set, the frequency of *BRCA1* mutations rose to 81% and *BRCA2* mutations fell to 14%. When both male and female breast cancer were seen in these families, the frequency of *BRCA2* mutations rose to 76%. Interestingly, families with more than five cases of female breast cancer were less likely to have a mutation in either gene. With more widespread testing in the high-risk clinics and population based studies, there remains a significant number of breast and/or ovarian cancer families without identifiable mutations in *BRCA1* or *BRCA2*. Lately, a number of these families have been shown to have large genomic rearrangements that were previously missed by coding region sequence analyses [26, 27].

BRCA1 is a large gene containing 5,592 nucleotides spread out over approximately 100,000 bases of genomic

Table 1. Summary of selected inherited adult cancer syndromes.

Syndrome	Primary tumor	Associated cancer or traits	Chromosome location	Cloned gene	Proposed function of gene product
Dominant syndromes:					
Li–Fraumeni syndrome	Sarcomas breast cancer	Brain tumors, leukemia, lymphoma	17p13.1	*TP53*	Transcription factor; response to DNA damage and stress, apoptosis
Familial adenomatous polyposis	Colorectal cancer	Colorectal adenomas duodenal and gastric tumors CHRPE, jaw osteomas and desmoid tumors (Gardner Sy) medulloblastoma (Turcot Sy)	5q21	*APC*	Regulation of β-catenin, microtubule binding
Hereditary non-polyposis colorectal cancer	Colorectal cancer	Endometrial, ovarian, hepatobiliary and urinary tract cancer, glioblastoma	2p16, 3p21, 2q32, 7p22, 2p16	*MSH2, MLH1, PMS1, PMS2, MSH6*	DNA mismatch repair
Hereditary diffuse gastric cancer	Gastric cancer	Lobular carcinoma, ?colorectal cancer	16q21–22	*CDH1*	Transmembrane cell adhesion molecule
Neurofibromatosis type 1	Neurofibromas	Neurofibrosarcoma, AML, brain tumors	17q11 2	*NF1*	GAP for p21 *ras* proteins; microtubule binding
Neurofibromatosis type 2	Acoustic neuromas, meningioma	Gliomas, ependymomas	22q12.2	*NF2* Links membrane	Proteins to cytoskeletons
Wilm's tumor	Wilm's tumor	Wilm's aniridia, genitourinary abnormalities, mental retardation	11p13	*WT1*	Transcriptional repressor
Beckwith–Wiedman syndrome	Wilm's tumor	Organomelaly, hemihypertrophy, hepatoblastoma, adrenocortcial cancer	11p15	*KIP2p57*	Cell cycle regulator
Nevoid basal cell carcinoma Sy	Basal cell skin cancer	Jaw cysts, palmar andplantar pits, medulloblastomas, ovarian fibromas	9q22.3	*PTCH*	Transmembrane receptor for hedgehog signaling molecule
Hereditary breast cancer 1	Breast cancer	Ovarian cancer	17q21	*BRCA1*	In a complex with Rad51 protein, repair of double stand breaks, transcription factor
Hereditary breast cancer 2	Breast cancer	Ovarian cancer, male breast cancer, pancreatic cancer, other?	17q21, 13q12	*BRCA2*	Directly interacts with Rad51 protein, repair of double strand breaks
Von Hippel–Lindau syndrome	Renal cancer (clear cell)	Pheochromocytomas retinal angiomas, cerebellar capillary hemangiomas	3p25	*VHL*	Regulates transcriptional elongation by RNA polymerase II
Hereditary papillary renal cancer	Renal cancer papillary type	Other cancers	7q31	*MeT*	Transmembrane receptor for hepatocyte growth factor
Familial melanoma	Melanoma	Pancreatic cancer, dysplastic Nevi, atypical moles	9p21, 12q13	*CDNK2A (p16), CDK4*	Inhibitor of CDK4 and cyclin-dependent kinases, cyclin-dependent kinase
Multiple endocrine neoplasia type 1	Pancreatic islet cell	Parathyroid hyperplasia, pituitary adenomas	11q13	*MEN1*	Regulation of *JUN-D* mediated transcription
Multiple endocrine neoplasia type 2	Medullary thyroid cancer	Type 2A pheochromatocytoma, parathyroid hyperplasia, type 2B pheochromocytoma, mucosal hamartoma, familial medullary thyroid cancer	10q11.2	*MEN2*	Transmembrane receptor, tyrosine kinase for glial derived neurotropic growth factor
Hereditary multiple exostoses (HME)	Exostoses (cartilaginous protuberances on bones)	Chondrosarcoma	8q24.1, 11p11–13, 19p	*EXT1, EXT2, EXT3*	Glycosyl transferases involved in synthesis of heparan sulfate
Cowden disease	Breast cancer, thyroid cancer (follicular type)	Intestinal hamartomas polyps, skin lesions	10q23	*PTEN, MMAC1*	Dual-specificity phosphatase with similarity to tensin
Hereditary prostate cancer	Prostate cancer	Unknown	1q25	Unknown	Unknown
Palmoplantar, keratoderma	Esophageal cancer	Leukoplakia	17q25	Unknown	Unknown

Table 1 Continued.

Syndrome	Primary tumor	Associated cancer or traits	Chromosome location	Cloned gene	Proposed function of gene product
Recessive syndromes.					
Ataxia telangiectasia	Lymphoma	Cerebellar ataxia, immunodeficiency, breast cancer in heterozygotes	11q22	*ATM* of p53	DNA repair, induction
Bloom's syndrome	Solid tumors	Immunodeficiency, small stature	15q26 1	*BLM*	Encodes DNA helicase, member of Rec Q family
Xeroderma pigmentosum	Skin cancer	Pigmentation abnormalities, hypogonadsim	Multiple complentation groups	*XPB, XPD, XPA*	DNA repair, helicases nucleotide excision repair
Fanconi's anemia	AML	Pancytopenia, skeletal abnormalities	9q22.3	*FACC*	DNA repair
			16q24.3	*FACC*	DNA repair
			others	*FACA*	DNA repair

Abbreviations: CHRPE – congenital hypertrophy of the retinal pigment epithelium; AML – acute myelogenous leukemia; GAP – guanosine triphosphatase-activating protein, a negative regulator of the p21 *ras* guanine nucleotide-binding proteins, contigous gene disorder – alterations in several distinct genes in a particular chromosomal region account for the phenotype seen in patients with the disorder; hedgehog – a secreted factor that regulates cell fate determination via its binding to the PTCH protein

Adapted from Fearon ER. Human cancer syndromes: Clues to the origin and nature of cancer Science 1997; 278: 1043–50.

DNA [24]. The gene is composed of 24 coding exons producing a protein of 1,863 amino acids. More than 700 mutations and sequence variations have been detected so far and only a few are recurrent in unrelated families [28]. Recurrent *BRCA1* mutations have been described in different European countries and in North America but the two most common are 185delAG and 5382insC [28]. *BRCA1* is a tumor suppressor gene thought to function by altering the expression of other genes and by participating in the cellular response to DNA damage [29, 30].

BRCA2

The second breast cancer susceptibility gene was localized to chromosome 13q12–13 in 1995 [31, 32]. This gene appears to be responsible for about 32% of hereditary breast cancers in families with at least four breast cancer cases in the family [20]. Several other cancers appear to be part of the *BRCA2* spectrum, including pancreatic, fallopian tube, laryngeal, uterine and male breast cancers as well as adult leukemia [33]. The *BRCA2* gene is composed of 27 exons distributed over roughly 70 kb of genomic DNA, encoding a protein of 3418 amino acids. More than 300 different mutations have been described in the *BRCA2* gene and only a few are recurrent [28]. One recurrent mutation 6174delT has a carrier frequency of 1.5% in Jews of Eastern European descent (Ashkenazi) while the recurrent mutation 999del5 accounts for a significant proportion of hereditary breast cancers in Iceland [34, 35].

Overall, inherited germline *BRCA1* and *BRCA2* mutations occur more frequently in families with multiple breast cancers, breast cancers along with ovarian cancers, both male and female breast cancers, and in individuals with early onset breast cancer (Table 2). However, *BRCA1* mutations have been detected in both healthy individuals and cancer patients with no significant family histories of cancer. These cases may reflect paternal inheritance of the mutation or low penetrance of the alleles involved. Additionally, patients may not be aware of their biological families' cancer histories, or may come from small families with few at risk individuals. Nonetheless, testing for *BRCA1/2* mutations should be offered only when indicated by a comprehensive risk assessment, and in the context of long-term clinical follow-up.

Clinico-pathological features of *BRCA*-associated tumors

BRCA-associated tumors have several features distinct from sporadic breast and ovarian tumors. BRCA1-associated tumors have a high frequency of aneuploidy and S-phase fraction, and are typically estrogen and progesterone receptor negative [36, 37]. Tubular and lobular cancers are more commonly seen in *BRCA2* mutation

Table 2 Criteria for referring patients for breast cancer risk assessment.

Patients should undergo genetic counseling for breast cancer susceptibility if the patient's family exhibits any of the following:

- Ashkenazi Jewish ancestry[a]
- Male breast cancer
- Personal history of bilateral breast cancer before age 50 years
- Personal history of breast and ovarian cancer
- Strong family history of breast and ovarian cancer among first-degree relatives
- Young age at breast or ovarian cancer onset (40–45 years)

[a] Familial breast and ovarian cancers have been studied in several ethnic groups but are best characterized in families of Eastern European origin

carriers. BRCA2-associated cancers are also more likely to be estrogen receptor positive [38, 39]. Hedenfalk and colleagues using DNA microarray technology have recently demonstrated that significantly different groups of genes are expressed by breast cancers with *BRCA1* mutations and breast cancers with *BRCA2* mutations [40].

One study has suggested that likely *BRCA* mutation carriers have higher rates of disease-free survival than control subjects with sporadic breast cancer [41]. However, this was a retrospective study performed without knowing the *BRCA* mutation status of the subjects using definitive molecular techniques. Subsequent studies using subjects with known *BRCA* mutation status have revealed that *BRCA1*-associated tumors were frequently high grade, and these studies report worse rates of disease-free and overall survival for *BRCA1* mutation carriers compared to non-carriers [41–43]. In a prospective cohort of 183 patients with invasive breast cancer, treated at the Institut Curie and presenting with a familial history of breast and/or ovarian cancer, tested for *BRCA1* germ-line mutation, those who had a *BRCA1* mutation (40 cases) had a worse outcome than those who did not; overall survival was poorer for carriers than for non-carriers (five-year rate, 80% vs. 91%, $P = 0.002$). Similar worse outcomes have also been reported in Ashkenazi Jewish women with *BRCA* mutations compared to non-carriers [43]. While the breast cancer mortality rates of *BRCA1* carriers may be worse, it has been observed that ovarian cancer patients with *BRCA1* mutations have higher rates of disease free survival than patients with sporadic cancer [44, 45].

Somatic *TP53* mutations are often associated with *BRCA1*-associated breast cancers [46]. Because tumor cells lacking both *BRCA1/2* and p53 have unstable genomes and are unable to repair genomic damage, these cancers may respond better than sporadic cancers to radiation and chemotherapeutic agents. This suggestion is consistent with the observation that ovarian cancer patients with *BRCA1* mutations have a significantly longer disease-free survival rate than sporadic cancer patients, specifically after receiving Cisplatin-containing treatment following tumor reduction surgery [44].

Thus, it is unclear from the literature whether women with *BRCA* mutations should be treated differently because they have a distinct form of breast cancer. Breast and ovarian cancers are associated with greater survival rates when they occur in younger women, so it is impossible to evaluate the effects of a specific treatment on *BRCA*-associated cancers *per se* without normalizing for age. While *BRCA*-associated cancers may theoretically be more sensitive to therapies that promote genomic damage, there have been no prospective randomized studies investigating whether conventional surgery, radiation and chemotherapeutic treatments are more or less effective in *BRCA* mutation carriers than in unselected breast and ovarian cancer patients. The challenge for the future will be to apply our understanding of the molecular functions of *BRCA1/2* to developing targeted therapies that are likely to be less toxic and more effective.

Genetic testing to quantify breast cancer risks

While demand for genetic testing for breast cancer has continued to rise in North America and Europe, there are no uniform criteria for offering these tests. Rather, the diffusion of genetic testing has largely depended on the socio-economic status of the patient or the availability of insurance coverage. In Europe, there appears to be a coordinated approach to provide cancer genetics services through organized 'Cancer Family Clinics' and in North America, the NCI has funded the Cooperative Family Registry for Breast Cancer Studies as well as the Cancer Genetics Network (www.cfr.epi.uci.edu). BRCA Analysis is now available as a clinical test at a cost of US$2,600 that is covered by most Insurance Carriers in the US. Nonetheless, physicians are encouraged to carefully select patients who are likely to benefit from genetic testing and such patients must be counseled regarding the risks, benefits and limitations of genetic testing for adult onset cancer.

Cancer can cluster in families purely by chance or as a result of shared environmental influences. A documentation of the types of cancers in a family should be obtained from medical records, pathology reports, and death certificates whenever possible in an effort to confirm the types of cancer that have occurred in the family. It is possible for a verbal report of cervical cancer to later be confirmed as ovarian or endometrial cancer, thus greatly altering the accuracy of the risk assessment. Examples of individuals likely to benefit most from *BRCA* testing and who should be offered genetic counseling and testing are listed in Table 2, but genetic testing should always be individualized and preceded by a comprehensive cancer risk assessment. A limitation of *BRCA* testing is that it does not detect all mutations in *BRCA1* and *BRCA2* and it misses other genes such as the recently localized *BRCA3* gene [47].

Management of high risk women

The cumulative risk of breast cancer for women with inherited mutations in *BRCA1* or *BRCA2* could be as low as 50% or as high as 87% by age 85 in some families [20, 33]. Likewise, the risk of ovarian cancer has been estimated to be anywhere from 15% to 60% by age 85 in some *BRCA1* carriers [20, 33]. In a population based study from Iceland, the penetrance for the 999del5 *BRCA2* mutation was estimated to be only 37% by age 70 [35]. The extreme variations in the penetrance of *BRCA1* and *BRCA2* add to the complexity of genetic counseling. While the efficacies of the different management options are not well defined, clinicians must provide some guidance to their patients during the decision making process. For patients who have already being

diagnosed with a curable first primary cancer, the risks of a second primary breast or ovarian cancer are substantial and should be factored into the management of the first cancer. In the US, current management options might include prophylactic surgery, intensive surveillance and participation in chemoprevention trials as listed in Table 3 [48–53].

Table 3. Management options for cancer prevention in women with *BRCA* mutations.

Surveillance/treatment option	Frequency
Breast self-examination	Monthly beginning at age 18
Clinical breast examination	Semiannually beginning at age 25
Mammography	Annually beginning at age 25
Pelvic examination	Semiannually beginning at age 25–35
Transvaginal ultrasound with Color Doppler and CA 125	Semianually beginning at age 25–35
Prophylactic bilateral mastectomy	Personal decision
Prophylactic bilateral oophorectomy	Personal decision

Modified from Burke W, Daly M, Garber J et al. Recommendations for follow up care of individuals with an inherited predisposition to cancer: BRCA1 and BRCA2. JAMA 1997; 227: 997–1003.

Prophylactic surgery

Recent studies have shown some benefit of a prophylactic mastectomy for select women. The strongest evidence comes from a retrospective analysis reported by Hartmann and colleagues from the Mayo Clinic. The authors studied 639 patients with family history of breast cancer who underwent prophylactic mastectomies between 1960 and 1993 [49]. The expected number of cancers in the patients was estimated with data from the biological sisters of the patients (high risk group) or with use of the Gail model (moderate risk group). In the moderate risk group (425 women), there was an 89.5% reduction in breast cancer incidence after prophylactic mastectomy while in the high risk group (214 women) there was a 90% reduction. A reduction in the predicted mortality rate was also demonstrated; the reduction was 100% for moderate-risk patients and 93% for high risk patients. In a recent update presented at the 91st Annual meeting of the American Association for Cancer Research, 29 of the 214 high risk women have been identified as *BRCA1* or *BRCA2* mutation carriers; none has developed breast cancer [50]. Thus, prophylactic mastectomy undoubtedly reduces the risk for breast cancer and remains a reasonable option for high-risk women. However, patients should receive extensive counseling including psychological evaluation prior to surgery since prophylactic mastectomy is an irreversible surgical option.

Bilateral total skin sparing mastectomy may be preferable to subcutaneous mastectomy in women who are genetically predisposed [51, 52]. Subcutaneous mastectomy removes only 90%–95% of the breast tissue, leaving the nipple-areola complex intact and may not be appropriate surgery for mutation carriers since any residual breast tissue remains at risk for the development of cancer. While there are no studies making a direct comparison between skin sparing and subcutaneous mastectomy, anecdotal reports suggest that women who develop breast cancer after a mastectomy were more likely to have been treated with subcutaneous mastectomy [49]. Cosmetic outcomes after prophylactic mastectomy are excellent and most women who undergo prophylactic surgeries are satisfied with their decisions. However, the irreversibility of the procedure and the fact that nipple sensitivity is invariably lost makes it a less appealing option for some women.

Bilateral oophorectomy before menopause can substantially reduce the risk of breast cancer. In *BRCA1* carriers, oophorectomy has been reported to reduce breast cancer risk (about 50%) as well as ovarian cancer risk (more than 80%) [53, T. R. Rebbeck personal communication]. Moreover, oophorectomy has been used in the adjuvant treatment of young women with breast cancer. Therefore, prophylactic oophorectomy has gained acceptance as a reasonable option for women at high risk after childbearing is completed. It may lower the risk of breast cancer while eliminating the risk of ovarian cancer [54, 55]. There are however reports of peritoneal carcinomatosis developing after prophylactic oophorectomy [56]. The complications of estrogen deficiency (e.g. osteoporosis) resulting from premature menopause after prophylactic oophorectomy in premenopausal women should be managed with hormone replacement therapy and continued until they reach menopausal age (50–55 years). The protection conferred by prophylactic oophorectomy does not appear to be lost after hormone replacement therapy [53].

Intensive surveillance

For women at high risk, current screening recommendations in the US include monthly breast self exams, physician breast examinations at four to six-month intervals and annual diagnostic mammograms beginning at the age of 30 or 5–10 years earlier than the youngest case in the family [48]. There is currently no data on the effectiveness of this approach to reduce breast cancer mortality in high risk women. A recent study suggested that tumors in *BRCA* carriers have the same radiological appearance as in non-carriers suggesting that yearly screening is likely to be effective [57]. Moreover, several studies have shown that 60%–90% of breast cancers diagnosed in young women are evident mammographically [58]. This suggests that routine screening in high risk women may lead to early detection and a decrease in breast cancer mortality. However, breast density is higher in younger women, and one small study has suggested that increased breast density in *BRCA1* car-

riers may hamper effective mammographic screening in these women [59]. In addition, a concern of women and physicians is that excessive radiation exposure may be harmful in women with BRCA mutations. Clinicians should therefore encourage their patients to participate in ongoing clinical trials that include the use of other imaging technologies such as Magnetic Resonance Imaging or Ultrasound as screening tools. However, until the clinical trials are completed, mammographic screening remains the only screening modality that has been shown to reduce breast cancer mortality among screened women and should probably be recommended.

Women with *BRCA1* or *BRCA2* mutations are also at increased risk for ovarian cancer but there is no screening test that can reliably detect ovarian cancer at an early stage. Transvaginal ultrasound plus CA 125 every 6–12 months are frequently recommended although there is no data to support their efficacy as screening tools [60].

Chemoprevention of breast cancer

Results of Tamoxifen as a chemoprevention agent has been controversial. In a recent study by the NSABP, Tamoxifen was shown to reduce the risk of breast cancer in high risk women from all age groups [16] but the effectiveness of Tamoxifen in *BRCA* mutation carriers has not been specifically studied. Moreover, two other studies, also including high risk women failed to demonstrate a reduction in risks for Tamoxifen users [61, 62]. However, a retrospective study among select women with *BRCA* mutations who received adjuvant therapy with Tamoxifen has documented a reduction in risk of contralateral breast cancer among BRCA carriers [63]. Thus, Tamoxifen may be a reasonable breast cancer risk reduction strategy, especially among *BRCA2* mutation carriers who generally tend to develop estrogen receptor positive breast cancers. Oral contraceptive use has been shown to reduce the risk of ovarian cancer in large population based series and a similar benefit has also been shown for BRCA carriers [64]. However, one small study has raised the possibility that oral contraceptives may be associated with an increased risk of breast cancer in BRCA mutation carriers [65]. In a retrospective study by Sellers and his colleagues from the Mayo clinic, women who have a family history of breast cancer and who used birth control pills before 1975 were shown to have an increased risk of breast cancer [66]. For women at risk for both breast and ovarian cancer, the potential benefit of 'modern' oral contraceptive pill in reducing the risk of ovarian cancer should be weighed against the slightly increased risk of breast cancer.

Colorectal cancer genetics

Recognition of hereditary forms of colon cancer makes it possible to target potentially life saving preventative interventions as well as offer the most appropriate treatment for individuals with cancer. Genetic predisposition plays a significant role in about 5%–10% of colorectal cancer cases [67–72]. The hereditary polyposis syndromes, adenomatous polyposis and hamartomatous polyposis syndromes, make up approximately one percent of the colorectal cancers diagnosed annually [67]. The hereditary non-polyposis colorectal cancer syndromes, (Lynch syndromes I and II) are believed to account for about 2%–4% of colon cancers [70]. A variety of case-control studies have consistently shown that a positive family history is a risk factor for colorectal cancer. The lifetime risk of cancer in the subgroups of familial or hereditary colorectal cancer syndromes varies from 15% risk in relatives of individuals diagnosed before the age of 45 years; through 20% for family members with two first degree relatives to approximately 70% to 95% in patients with FAP and HNPCC [68, 70]. The American Cancer Society and the American Gastroenterological Association recently added a new risk category for colon cancer screening based on the consistency of the data in numerous studies [71, 72]. Individuals with a family history of colon cancer are encouraged to begin screening at age 40 (rather than age 50, as recommended for the general population). While these recommendations have not been universally accepted, what is more important is that physicians recognize individuals most at risk for hereditary colorectal cancer.

Familial adenomatous polyposis (FAP)

FAP is an autosomal dominant syndrome characterized by multiple polyps (>100) in the colon and rectum, usually hundreds or thousands of adenomatous polyps throughout the colon [67, 73]. The incidence is 1/8,000 but it is the most clearly defined and well understood among the inherited colon cancer syndromes. The average age of patients at the onset of polyps is 25 years, at the onset of symptoms (gastrointestinal bleeding, and abdominal pain) 33 years, at diagnosis of polyposis 35 years, and at diagnosis of colon cancer, 42 years. Over 90% of cases of FAP are identified by the age of 50. Extracolonic manifestation of FAP include multiple mandibular osteomas, desmoid tumors, duodenal and gastric adenomas, thyroid tumors, adrenocortical and brain tumors and congenital hypertrophy of the retinal pigment epithelium (CHRPE). *Attenuated FAP* (AFAP) differs from the classical form in the number (usually <100) and localization of adenomas (proximal to the splenic flexure) as well as age of onset which is usually later than classical FAP (around 55 years of age) [74]. The genetic locus for FAP was mapped to chromosome 5q21–22 in 1987 and the *APC* (adenomatous polyposis coli) gene was cloned in 1991 [75, 76]. The most common mutations in the *APC* gene are point mutations and microdeletions, that lead to the synthesis of a truncated protein [77, 78].

Genetic testing for FAP and AFAP

Both FAP and AFAP can be diagnosed by testing for germline mutations in the *APC* gene. Majority of FAP families have protein truncating mutations in the *APC* gene and a protein truncation assay is widely used to identify mutations [79, 80]. This method is sensitive enough to detect about 80% of known *APC* mutations. Once a mutation is known in a family, the same mutation is transmitted from generation to generation in the given kindred. Thus, testing for the *APC* genetic alteration can be confined to the particular region of the gene once the mutation has been identified in an index patient. Genetic testing for APC mutations is now considered standard of care for FAP families. This is because presymptomatic genetic testing removes the necessity of annual screening of those at-risk individuals who do not have the gene mutation, and may increase adherence to screening recommendations in those who have the gene mutation.

The *APCI1307K* missense mutation is the basis for a form of familial CRC that has recently been described [81, 82]. The mutation is found in 6% of the general Ashkenazi Jewish (Eastern European) population and explains an undefined proportion of familial CRC in this ethnic group. Individuals with this mutation have an increased lifetime risk of CRC with estimated odds ratio of 1.4 to 1.9. The clinical application of this mutation remains ill-defined but genetic testing for this allele is now commercially available.

Management of patients with FAP or AFAP

Individuals who inherit a mutated *APC* gene have an increased risk of developing colorectal cancer and all primary relatives of FAP patients should be offered screening and genetic counseling. The penetrance has been estimated to be almost 100% [77–80]. Those at highest risk are individuals who have a sibling, parent, or whose children manifest the phenotype. Conventional management of persons at increased risk for developing FAP has been to initiate early colon surveillance by sigmoidoscopy or colonoscopy by age 12 (Table 4). The procedure is repeated every one to two years if polyps are found. If polyp negative at age 12, the frequency of colonoscopy might be reduced but many groups would still advocate flexible sigmoidoscopies every one to two years. Surgical therapy is the only acceptable option for patients with FAP after colonic polyps are detected but the timing of colectomy should be individualized based on tthe numbers of polyps found. One study has suggested that the type of mutation identified may influence the timing of surgery but this remains controversial [78]. There is a relatively long time span from the average age of polyp onset (age 15) to the average age of colon cancer diagnosis in FAP (age 42). Thus, endoscopic surveillance is the preferred management following genetic testing in children. Surgery is delayed whenever possible until the child reaches his or her 20s [79]. However, once numerous polyps are found (irrespective of age), surveillance colonoscopy is no longer useful and colectomy may be warranted. Rectum-sparing surgery with sigmoidoscopic surveillance of the remaining rectum is a reasonable alternative to total colectomy in FAP patients.

Table 4 Surveillance Protocol in FAP and HNPCC.

Genetic testing in familial colorectal cancer			
Disorder	Lower age limit (years)	Examination	Interval (years)
FAP	12	Colonoscopy/sigmoidoscopy	2
	25–30	Gastroduodenoscopy	1–2
	After colectomy	Rectoscopy	1–2
HNPCC	20–25	Colonoscopy	1–2
	30–35	Gynecologic examination transvaginal ultrasound	1–2
	30–35	Gastroduodenoscopy[a]	1–2
	30–35	Abdominal ultrasound, cytology urine[b]	1–2

[a] If gastric cancers runs in the family.
[b] If urinary tract cancers (renal pelvis, ureter) cluster in the family.

Penetrance for APC mutations is nearly 100%, However in a family with a known *APC* mutation, if no polyps are found in a gene carrier, colonoscopy may be repeated every 2–3 years until the patient reaches the age of 40. It is not indicated to surgically remove polyp-free colons even in mutation carriers. Most patients who have the mutated *APC* gene manifest colonic polyps by age 30. Unfortunately, there is no hard core scientific evidence for the upper bound age limits when no polyps are found in at risk individuals. However, since colorectal cancer is common in the general population, even in the absence of polyps, these patients are encouraged to follow American Cancer Society colon cancer surveillance recommendations for the general population after age 40 years [71]. Because of the increased risk for polyps, upper gastrointestinal endoscopic surveillance is usually recommended as part of research protocols. Whether it should be routinely performed to screen for duodenal or periampullary cancer is controversial but there appears to be survival advantage for individuals who undergo surveillance and surgery for duodenal polyposis [83].

Individuals who test negative within a family with a known mutation have the general population risk for colon cancer and need no additional screening. Nonetheless, some programs recommend a baseline sigmoidoscopy by age 35 years [80].

Polyp prevention studies

Sulindac, a nonsteroidal anti-inflammatory agent has been shown to lead to the regression of polyps in limited animal studies, anecdotal reports and in one randomized controlled clinical trial [84]. In these studies, a decrease in the number and size of polyps was seen before and after colectomy but the polyps were not completely eradicated. Therefore, it is unlikely that Sulindac will substitute for colectomy. Further clinical studies including COX-2 inhibitors are ongoing to develop new chemoprevention agents for FAP patients. As dietary factors such as resistant starch have been shown to have a inverse correlation with colon cancer incidence, a European double blind trial is currently under way examining the effect of Aspirin and/or resistant starch on the prevention of appearance or progression of polyps in FAP patients [85].

Hereditary non polyposis colon cancer (HNPCC)

Unlike FAP, patients with HNPCC do not have an unusual number of polyps and often have a solitary colorectal tumor. It is estimated to account for about 5% of all colon cancers [67]. HNPCC is also known as Lynch syndrome Type I and II or Cancer Family syndrome. It is inherited in an autosomal dominant fashion with variable penetrance [86–88]. HNPCC should be suspected if there are early onset colon cancers in an extended family, predilection to the proximal or right-sided colon and an excess of synchronous and metachronous cancers. Type II disease is distinguished from Type I by the presence of extracolonic cancers, including cancers originating in the uterus, ovary, ureter, renal pelvis, stomach, pancreas, biliary tree, bone marrow, skin, and larynx [86]. The average age at CRC diagnosis is 44 years compared to 64 years in sporadic CRC. Unlike sporadic cancers, which develop most often on the left side of the colon, HNPCC cancers are most likely to develop on the right side, defined as proximal to the splenic flexure. In addition, mucinous and signet cell carcinomas are common. Recently, undifferentiated medullary or solid cribriform carcinoma has also been described as a manifestation of CRC in HNPCC. Another interesting finding is the presence of tumor-infiltrating lymphocytes as well as a Crohns disease-like reaction and peritumoral lymphocytic infiltration [87] which could represent an immune reaction and provide an explanation for the known survival advantage in HNPCC associated colon cancers.

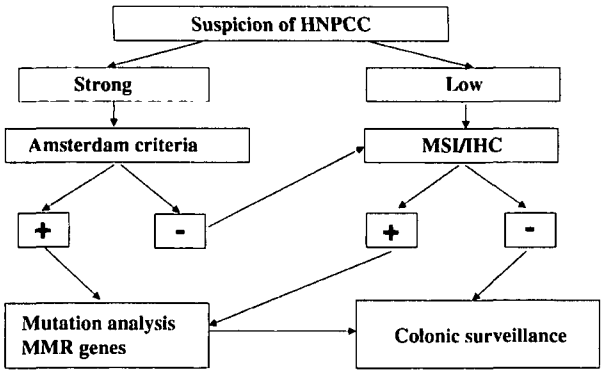
Genetic testing for HNPCC

Criteria for genetic testing for HNPCC in the clinical setting are not very clear. The research criteria for HNPCC families were first established by the International Collaborative Group (ICG) meeting in Amsterdam in 1990, and are known as ICG or Amsterdam criteria [88]. These criteria are useful when reviewing a family history and include: 1) one member diagnosed with CRC before age 50, 2) two affected generations; and 3) three affected relatives, one of them a first degree relative of the other two, FAP is excluded. While these criteria provide a general approach to identifying HNPCC families, they are not considered to be completely inclusive. In clinical practice, the Amsterdam criteria has been less useful because the criteria do not take other tumor types into account and families meeting this criteria only represent 0.3%–2% of CRC patients in population based studies. In 1997, new criteria which include adenomas as well as extracolonic HNPCC associated tumors and histologies was proposed as a basis for microsatellite testing candidacy in suspected HNPCC families [89]:

1. The existence of three or more relatives with histologically verified CRC, one of whom is a first-degree relative of the other two.
2. Colorectal cancer involving at least two generations.
3. One or more cases of CRC diagnosed before the age of 50 in the family.
4. Patients with two HNPCC-related tumors (colon, endometrial, ovarian, ureteral cancer).
5. Patients with CRC or with first degree relative with HNPCC-related cancer; one of the cancers at < 45 years or adenoma < 40 years.
6. Patients with CRC or endometrial cancer < 45 years, especially if right-sided CRC or with typical pathology.
7. Patients with adenoma < 40 years.

HNPCC is caused by mutation in one of several DNA mismatch repair genes [100–101]. These genes function to maintain the fidelity of DNA during replication. At least five different mismatch repair (MMR) genes have been identified in association with HNPCC. Genetic linkage of HNPCC was first shown to a region on chromosome 2 in two large kindreds with HNPCC [90]. The gene on chromosome 2 has been identified as a DNA-mismatch-repair gene, human homolog of the prokaryotic mutS gene, *hMSH2*. Other human homologues of the prokaryotic DNA-mismatch-repair gene *mutL* have been identified and are: *MLH1* (on chromosome 3), *PMS1* (chromosome 2q31–33), and *PMS2* (chromosome 7p22) [91–93]. All these genes are mutated to a variable extent in the germline of patients with HNPCC. Recently Miyaki et al. [95] detected a germline mutation of *hMSH6* in one of five Japanese families with HNPCC in which no mutations of *hMSH2* or *hMLH1* had been found. *hMSH2* or *hMLH1* are each mutated in about 30% of the cases while *PMS1* and *PMS2* are mutated in less than 5% of the cases.

MMR deficiency gives rise to microsatellite instabilities (MSI). Microsatellites are repetitive non-coding DNA sequences of yet unknown function that are found throughout the genome. Microsatellites can also be found in the coding regions of genes and MMR deficiency can



MSI, microsattelite Instability; IHC, immunohistochemistry, MMR, mismatch repair

Figure 1 Genetic testing for HNPCC.

lead to mutations in critical genes such as *APC* or *KRAS* that are involved in tumor initiation or progression. Molecular studies in patients with HNPCC have shown that more than 90% of tumors have genetic changes indicative of errors in DNA replication on several chromosomes [96]. Therefore tumor specimens from putative HNPCC patients can first be examined for the presence of MSI using markers from different chromosomal regions. Mutation analysis is often recommended after tumor evaluation for MSI is positive because tumor DNA that shows alterations in microsatellite regions indicate probable defects in MMR genes. In addition, immunohistochemistry using antibodies directed at the different proteins could be helpful in deciding which particular gene to screen for. As an example, a patient with high MSI and lack of MLH1 protein expression in the tumor is likely to harbor a germline mutation in the *MLH1* gene. Thus,a protein truncation assay for the MMR gene *hMLH1* is then performed on RNA extracted from a blood sample of the patient. The nature of the truncating mutation is determined by sequencing and screening for the specific mutation could then be offered to at risk family members. Genetic testing for HNPCC is limited by the fact that existing tests fail to detect mutations in as many as 20%–30% of individuals who have the typical form of HNPCC. The current sensitivity for genetic testing is only 50%–95% depending on the methodology used.

Screening for mutations in MMR genes is both time consuming and expensive, given the heterogeneiety in the spectrum of mutations in all five genes. Thus, MSI screening has been evaluated as a cost-effective way to select patients for testing by Aaltonen and colleagues in a population based series of 509 colorectal cancer cases from Finland [97]. Sixty-three tumors (12%) showed MSI, and 10 of these patients had a germline mutation in *MSH2* or *MLH1*. Nine of the mutation carriers had a first degree relative with colorectal cancer or endometrial cancer, seven were younger than 50 years, and four had a colorectal or endometrial cancer previously. Similar findings have been reported by other groups, hence the current recommendation to begin testing with MSI analysis combined with immunohistochemical analysis of the tumor specimens. Even though 15% of tumors associated with *MSH2* or *MLH1* mutations are MSI-low or MSI-stable, MSI analysis is still a cost-effective way to select families for genetic testing. It should be noted that families with *MSH6* mutations tend to have a higher frequency of endometrial cancers and display lower and later penetrance of colorectal cancer. Moreover, the tumors are frequently MSI-low or MSI-stable. A recent study reported *MSH6* mutations in four of 18 Dutch families with suspected HNPCC who had MSI-low or MSI-stable tumors [98]. An algorithm for genetic testing which incorporates MSI screening in suspected HNPCC patient is illustrated in Figure 1.

Management of HNPCC

To provide optimal care for HNPCC families, a multidisciplinary approach is recommended because of the complexities involved in identifying at risk individuals, interpreting test results and discussing the clinical implications of a positive test. A multidisciplinary expert panel recently provided specific recommendations for screening and surveillance of individuals with an average or elevated risk of colorectal cancer (Table 4) [99–101]. Patients with a history suggestive of HNPCC should receive genetic counseling and be screened for mutations in MMR genes. Individuals who test positive for a deleterious mutation should have a colonoscopy every 1 to 2 years starting between the age of 20 and 25 years and every year after age 40 years. Patients with HNPCC with curable colorectal cancer should have a subtotal colectomy because synchronous or metachronous colon cancers occur in 35% of patients. Because the risk of developing rectal cancer is approximately 12% in the first 12 years after subtotal colectomy the rectum should be examined annually by sigmoidoscopy [99].

While the lifetime risk for colorectal cancer is 70% to 85% for *hMLH1* and *hMSH2* mutation carriers, prophylactic subtotal colectomy is usually not recommended because of the increased risk for other cancers e.g. endometrial cancer (50% lifetime risk) and other extracolonic cancers (about 15% lifetime risk) [100–102]. Female HNPCC mutation carriers have increased risk of endometrial cancer as well as ovarian cancer, therefore, endometrial and ovarian cancer screening may be warranted (Table 4). Unfortunately, there is no effective way to prevent cancer in mutation carriers. In addition, for families with urinary tract cancers, screening with abdominal ultrasound and urine cytology may be warranted.

Importance of a coordinated multidisciplinary approach to cancer genetic counseling

Genetic testing for adult-onset disorders raises numerous ethical, legal, and social concerns such as adverse psy-

chological consequences for the individual and his/her family, loss of insurance or employment, and social stigmatization [1–4]. Informed consent must be given in accordance with published guidelines on genetic testing [1–4]. In order to give informed consent a patient must understand the advantages, disadvantages, risks, limitations and consequences of genetic tests. The impact of genetic testing on an individual depends on their perceived risk of cancer, personal experiences with cancer, understanding of cancer, self-image, and social and family relationships. All these factors should be evaluated before genetic testing. Recent studies have shown that the uptake of genetic testing in families with HNPCC varied widely, from 43% in the US to 75% in Finland [104]. One reason for the differences might be related to differences in the health care and social security systems in the US and Europe. In breast cancer families, test uptake correlates with socioeconomic status and the educational background of the women [105, 106]. One feature that seems to be common to breast cancer family clinics in several countries is a strong bias towards higher social class among individuals seeking genetic testing [106]. More work is needed to examine the special needs of low social class individuals and ethnic minorities.

Genetic testing may have adverse psychological consequences and social risks and it should be undertaken in multiple steps. The likelihood of adverse psychological response to genetic testing must be evaluated during the pre-test counseling process and before blood is drawn for testing. To date, most studies have failed to document serious adverse effects in individuals who choose to know their mutation status [104, 106–108]. Most significantly, one study has concluded that individuals with strong family histories of breast and ovarian cancer experience higher levels of cancer-related stress and depression by choosing not to participate in an educational session to learn their mutation status [106]. Darval et al., in a recent study, assessed the ability of individuals who undergo genetic testing for cancer susceptibility to accurately anticipate emotional reactions to disclosure of their test results [108]. They found that in general, patients that did not have a personal history of cancer were fairly accurate in predicting their responses to test results. Interestingly, cancer patients tended to underestimate their reactions to receiving their test results and experienced more distress than anticipated. These data underscore the importance of providing adequate pre and post test counseling for patients who are contemplating genetic testing. Resources for psychological counseling should be readily available to individuals who are identified as high risk.

Prophylactic surgery remains a viable option for *BRCA* mutation carriers but such women should have consultation with surgeons (breast and reconstructive surgery) and be extensively counseled about the potential outcomes prior to surgery. A recent study completed in the Netherlands demonstrated that 48% of young women included in the study who were at 50% risk to have a *BRCA* mutation requested DNA testing; 51% of these women who were eligible for prophylactic surgery, decided on prophylactic mastectomy and 64% opted for oophorectomy. Additionally, the authors found that age, having children, and high pre-test risk were positively associated with the decisions to undergo testing and prophylactic surgery [109]. In another study from Australian, the intention to undergo prophylactic mastectomy after receiving a positive mutation result was found to directly correlate with a woman's degree of breast cancer anxiety [110]. It is therefore important for health care providers to incorporate the psychosocial aspects of genetic testing and cancer screening in their management of high risk families.

The complexities of genetic counseling for cancer make it time consuming and not compatible with general or mainline oncology practice. Hence, many academic centers in the US and in Europe have developed specialized programs in clinical cancer genetics that are multidisciplinary in approach and involve the participation of genetic counselors, nurse specialists, social workers, psychologists, surgeons/gynecologists, radiologists and physicians with expertise in cancer genetics. It is no longer sufficient to refer patients to established medical genetics clinics where there is no provision for a coordinated mechanism for follow up of the patients e.g. ensuring that high risk women get annual mammography and other cancer screening tests. Therefore, oncologists are encouraged to embrace the concept of cancer family clinics that serve multiple purposes including ascertainment of cases, risk assessment, genetic counseling and testing, coordination of longitudinal follow up and responding to the psychosocial needs of family members. As genetic testing for common cancers such as breast, or colon become standard of care, oncologists are encouraged to assume the responsibility of coordinating the care of their patients and their at risk family members.

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