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Applications of Advances in Molecular Biology and Genomics to Clinical Cancer Care

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Genetics technologies, methods, and discoveries are being integrated rapidly into medical and nursing practices in a variety of ways. The purpose of this article is to familiarize nurses with how new genetic technologies and discoveries are being incorporated into various phases of clinical oncology practice. The scope of this article is broad to provide an overview of the ways in which cancer prevention, surveillance, diagnosis, prognosis, monitoring, treatment, and gene therapy are evolving due to advances in the molecular biology of cancer. We use specific examples to demonstrate the use of genetic information to achieve these objectives and to illustrate principles and strategies that may be applied to a variety of cancers.

■ Introduction

The practice of medicine, in all disciplines, is changing as a result of the rapid advances in molecular biology and genomics. With the initial sequencing and analysis of the human genome complete, further advances in the understanding of genetic mechanisms underlying cancer will undoubtedly occur.^{1,2} Although some people considered achieving the initial sequence to be the end of the genome project, others believe that we are only now entering the true genome era, where the availability of genetic information will help us unlock biological processes more efficiently and lead to translation of this knowledge into improved clinical care.³

Nowhere are the changes due to advancing genetic knowledge more profound and widespread than in oncology.⁴ Here we are already seeing incorporation of genetics into all phases of cancer care as enumerated in Figure 1. Although the focus of this article is on the current standard of care in oncology, a preview into future trends in oncology is also included.

Some of the ways that an understanding of cancer at the molecular level will improve cancer management is by allowing for:

- a better understanding of cancer etiology and risk
- selection of well-defined population screening, prevention, and treatment trials
- increased accuracy and specificity for prevention, diagnosis, surveillance, treatment, and prognostic information

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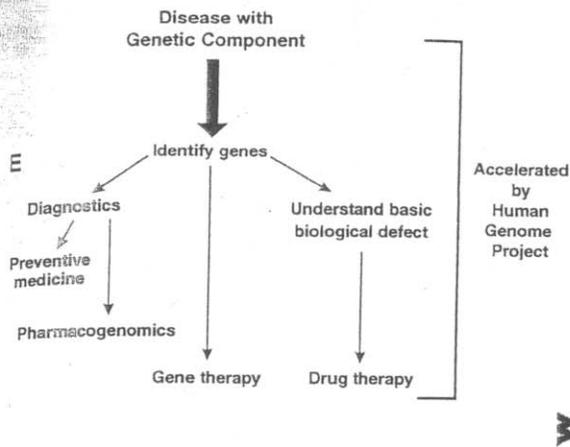


Figure 1. Incorporation of genetics into all phases of cancer care.

- modification of standards in risk reduction, medical surveillance, and treatment options for those with genetic predisposition to cancer as defined by genetic susceptibility testing (includes approaches to primary and secondary prevention)
- understanding of the molecular biology of cancer leading to rational therapeutic design of treatments for cancer, including the development of gene and drug therapies for specific molecular targets

■ Genetic Influence of Individual Cancer Susceptibility

Cancer involves the progressive disruption of the genetic material in cells of the target organ, which results in malignant transformation.⁵ This process is often broken down into the stages of initiation, promotion, and progression. Most of these alterations are somatic, occurring only in cells of the target organ. Long latency periods exist between carcinogenic exposure and disease development related to the accumulation of multiple genetic mutations for many of the common cancers of late adulthood. Some genetic alterations are inherited, occurring in every cell in the body, including the gonadal germ cells, and, therefore, can be passed on to future generations.⁶ Retinoblastoma provides an example that distinguishes between cancers related to germline, or inherited, mutations and cancers related to spontaneous mutations.⁷ Retinoblastoma is a tumor that develops in the retinal cells of the eye. Approximately half the cases are sporadic, and half of the cases occur in an inherited autosomal-dominant fashion. In the inherited cases, the tumors develop in both eyes, at very young ages and frequently have more than one tumor in each eye. In the sporadic cases, the disease usually occurs at a later childhood age and involves only one tumor in one eye. As the understanding of the molecular biology of carcinogenesis increases, the ability to identify high-risk groups and develop specific strategies for risk reduction in these groups increases.

Knowledge of genetic mechanisms underlying carcinogenesis provides new opportunities for cancer prevention. The overall goal of carcinogenesis research is to understand the processes involved in cancer induction so that specific interventions may be precisely developed to prevent the disease from occurring. Hursting and colleagues suggest a stage-specific approach to prevention strategies and the molecular changes targeted within each stage.⁸

■ The Impact of Individual Genotypes on Moderately Increased Cancer Susceptibility

People are genetically heterogeneous when it comes to cancer susceptibility. Certain individuals are more susceptible than others to specific cancers or to cancer in general. Two people exposed to the same agent may have very different risks of cancer on a biologic basis and, therefore, react differently both to carcinogen exposure and to risk-reduction methods. This is known as individual susceptibility, and it may have its basis in differences in:

- carcinogen uptake, activation, and detoxification
- deoxyribonucleic acid (DNA) repair variations
- inherited or acquired mutations in specific proto-oncogenes or tumor suppressor genes
- nutritional status
- hormonal profile
- immune function

Genetic variations in carcinogen metabolism represent an important mechanism by which members of the general population differ in their susceptibility to cancer.⁹ Although some cancer risk factors, such as ionizing radiation and various specific carcinogens, can damage DNA, many carcinogenic substances require metabolic activation from a precarcinogen to an active carcinogen to alter the DNA. This conversion of a benign chemical substance into a highly reactive form is controlled by certain groups of enzymes, many in the cytochrome p450 family. There is variability among individuals in the function and activity of these enzymes, which in turn, may lead to alterations in the rate at which carcinogens are activated. This variability is believed to account for significant interindividual differences in cancer susceptibility.

Other enzyme systems are involved in the detoxification of already-activated carcinogens, and these, too, vary in efficiency and speed, which may permit highly reactive carcinogen molecules to remain biologically active for longer than usual periods of time. It has been suggested that "slow metabolizers" of carcinogens may be at increased risk of cancer as a consequence of this phenomenon.⁹ There are also genetic variations in the cellular mechanisms that repair DNA directly damaged by certain carcinogens. Combinations of these different mechanisms of carcinogen activation, detoxification, and DNA repair may lead to individual differences in cancer risk and development.

A prototypical example of a gene that alters cancer risk by controlling hereditary variation in metabolic activation/inactivation is the human acetylator trait (*NAT2*) and bladder cancer. In Western populations there is an approximate 50-50 split between slow acetylators (homozygous for the deficient acetylation allele) and fast acetylators. Carcinogen action depends on a dynamic balance of metabolic activation and elimination; slow acetylators are inefficient in eliminating the active form of the chemical. Carcinogenic aromatic amines include 4-amino biphenyl, benzidine, and 2-naphthylamine and account for increased bladder cancer in dye workers and tobacco smokers. The early population studies involving acetylation required laborious "phenotype" assays with administration of caffeine, dapsone, or other probe drugs metabolized specifically by these genes. As the N-acetyltransferase gene (*NAT2*) was cloned in the late 1980s and the genetic basis of the observed difference in enzymatic activity was identified, genotype assays on DNA supplanted drug probes.¹⁰ Meta-analyses of *NAT2* "slow acetylators" and bladder cancer¹¹ consistently demonstrate increased risk for slow acetylators and a formal gene-environment interaction has also been demonstrated.¹² That is, cigarette smokers, who have greater aromatic amine exposure, exhibit an additional increment of risk if they possess the slow acetylation genotype/phenotype.

■ The Impact of Individual Genotypes on High Risk of Cancer Susceptibility

Thus far, the discussion has centered on inherited differences in the abilities to handle a variety of exogenous environmental risk factors. Other individuals at high risk of cancer are those who have inherited a mutation in an autosomal-dominant cancer susceptibility gene. Clinical suspicion regarding one of these hereditary syndromes is based on either family history or disease-related characteristics, such as specific benign hamartomas of the face, tongue, soles, and palms in Cowden syndrome.¹³ Once this suspicion has been raised, presymptomatic testing in search of germline mutations in the gene related to the suspected disorder may or may not be available to confirm the diagnosis on a molecular level. It is important to attempt to recognize these syndromes whenever possible because all phases of medical management of the individual and his or her relatives may be altered significantly. The general issues related to hereditary cancer susceptibility and genetic testing have been covered elsewhere.^{14,15} Individuals with inherited cancer susceptibility syndromes, such as breast and/or ovarian cancer due to *BRCA1* and *BRCA2* mutations, Li Fraumeni syndrome (LFS), hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), multiple endocrine neoplasias (MEN), and von Hippel Lindau (VHL) syndrome, are at significantly increased risk of developing specific constellations of cancers. Once at-risk patients understand how knowing their mutation status might affect their healthcare, they may become interested in cancer-risk assessment, clinical genetic testing, and risk-reduction recommendations.

■ Primary Cancer Prevention in the General Population and in Genetic High-risk Populations

The goal of primary cancer prevention is to identify factors that place individuals at risk of developing cancer and to reduce the risk factors that are modifiable, thus lowering the risk of cancer. Modifiable risk factors may include lifestyle exposures (eg, diet, smoking, alcohol use, and reproductive decisions) and environmental exposures (eg, air, water, soil, and food pollution). Primary risk factors that are not modifiable include age, family history of cancer, and gender. For the general population, primary cancer prevention encourages avoiding tobacco, limiting or eliminating alcoholic beverages, using sunscreen during sun exposure, exercising regularly (30 minutes a day on most, if not all, days of the week), eating a well-balanced diet (including 5 fruits and vegetables a day), and chemoprevention for select groups who are at high risk of cancer. For more information on the American Cancer Society's healthy lifestyle recommendations primary cancer prevention, visit its Web site at <http://www.cancer.org>.

For individuals at high risk of cancer due to genetic susceptibility, the primary cancer prevention options include lifestyle modification, risk-factor reduction, chemoprevention, and prophylactic surgery. There are insufficient scientific data from prospective randomized controlled clinical trials to permit evidence-based prevention recommendations in hereditary breast and colon cancers. Most risk-reduction strategies are currently based on common sense, biologic plausibility, and best clinical judgment.^{16,17}

■ Lifestyle Modification in the Genetic High-risk Populations

In the realm of primary cancer prevention, there are several preliminary studies that suggest that there may be an association between lifestyle factors, inherited predisposition to cancer, and cancer risk. Vachon and colleagues¹⁸ evaluated the interaction of alcohol consumption and breast cancer risk among women with a family history of breast cancer. They found that daily drinkers had a relative risk of breast cancer of 2.45 compared with never drinkers among first-degree relatives of a person with breast cancer. Jernstrom and colleagues¹⁹ evaluated breast-feeding patterns and breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. They reported that *BRCA1* carriers who had breast-fed for more than 1 year experienced a significant reduction in their odds ratio (OR) of breast cancer—0.64 (95% confidence interval 0.38-1.09). Breast-feeding did not confer protection against breast cancer among *BRCA2* mutation carriers. The results of both of these studies are preliminary and do not represent data from prospective randomized clinical trials, the gold standard for establishing prevention strategies. In general, it is prudent to avoid basing major changes in clinical practice on the results of a single study.

■ Prophylactic Surgery in Genetic High-risk Populations

The use of prophylactic surgery is considered appropriate for carefully selected individuals with specific hereditary cancer syndromes. The rationale for surgery is that by removing an organ at risk of developing cancer, a person will lower his or her individual cancer risk. For example, early surgical removal of the polyp-filled colon from patients with FAP prevents invasive colon cancer.²⁰ Likewise, prophylactic removal of the thyroid in persons affected with MEN2 has become the standard of care since medullary thyroid carcinoma or its precursor lesion, C-cell hyperplasia, is found in nearly 100% of studied individuals with MEN2.^{20,21}

Unfortunately, surgical prophylaxis has its limitations and shortcomings. For example, prophylactic colectomy sometimes triggers the development of desmoid tumors in FAP patients.²² These biologically aggressive soft-tissue tumors are a source of great morbidity in this setting. In VHL, patients develop multiple bilateral renal cysts and tumors over time. If allowed to go untreated, these have a strong probability of evolving into renal cell carcinomas. The optimal treatment of these renal lesions is controversial,²³ because if one performs total resection of the kidneys at initial diagnosis of cysts or pre-malignant tumors, then patients may require chronic dialysis or kidney transplantation. On the other hand, subtotal resection of cysts and removal of individual tumors can prolong the kidney function but subject the affected person to repeated major surgeries. Although both approaches have extended survival of affected individuals, none of these options is completely satisfactory.

In the case of hereditary breast cancer risk, prophylactic removal of one or both breasts does not result in removal of all breast tissue. Therefore, a woman may reduce risk to an unknown degree but still has some residual risk of developing breast cancer. A recent retrospective (but nonrandomized) study of 139 women with either a BRCA1 or a BRCA2 mutation evaluated the incidence of breast cancer in those women who elected to have prophylactic mastectomy and those who elected to have regular surveillance.²⁴ Seventy-six of these women had prophylactic mastectomy (PM), and 63 had regular surveillance. At 3 years (3.0 ± 1.5 years) of follow-up, none of the women who elected for PM had developed breast cancer, whereas 8 breast cancers had developed among women who declined surgery, choosing surveillance instead. Prophylactic surgery is offered as an option to be carefully considered in the context of personal and cultural values and careful multidisciplinary consultations.^{24,25}

The situation is even more daunting for women at genetic risk of developing ovarian cancer. In contrast to the options that exist relative to breast cancer or colon cancer, medical surveillance for ovarian cancer is ineffective. Furthermore, because this disease often presents at an advanced clinical stage, survival rates for ovarian cancer are generally less favorable. Therefore, the woman at elevated risk of ovarian cancer has more motivation to consider prophylactic surgery. The degree to which this proce-

dures reduces the risk of ovarian cancer is not well studied, although one recent report suggested a 96% reduction in risk.²⁶ However, there are published reports of malignancy occurring in the peritoneal lining (which has the same embryonic origin as the ovaries) after women have undergone prophylactic oophorectomy.²⁷ The resulting malignancy, called primary peritoneal carcinoma, is histologically and clinically similar to ovarian cancer in its characteristics. Although this phenomenon certainly must be described to women who are contemplating prophylactic salpingo-oophorectomy, its occurrence is a relatively rare event, the frequency of which has been overstated in the clinical cancer genetics literature. On the benefit side of this decision, a recent study has suggested that oophorectomy lowers the risk of breast cancer (by approximately 50%), probably by lowering the estrogen levels within a woman's body.²⁶

Another important limitation of risk-reduction measures in persons with inherited predisposition to cancer is that the increased risk is rarely confined to a single organ system. HNPCC provides a vivid illustration of the difficulties that result from this reality.²⁸ Persons with an inherited HNPCC gene mutation are at risk of developing multiple colorectal cancers. Some people with the gene mutation may choose to have the colon removed at the time of diagnosis of the first tumor to prevent additional tumors that are likely to occur. However, these same individuals are also at risk of endometrial and ovarian cancer, as well as tumors of the upper gastrointestinal tract and upper urinary tract. The multiplicity of organs at risk of malignant transformation, and the widely varying lifetime risks of developing each of these syndrome-related cancers, makes it very difficult to formulate a primary cancer prevention strategy for these patients.

■ Chemoprevention in the General Population and in the Genetic High-risk Populations

The term *chemoprevention* has been used for several decades to refer to the use of natural or synthetic compounds to prevent, reverse, or delay the development of cancer in otherwise healthy individuals with risk factors for malignancy or with precancerous conditions.²⁹ This field is based on elucidating the factors that influence molecular changes involved in cancer initiation, promotion, and progression so that new agents can be developed that block these transitions before the emergence of an invasive or clinically detectable cancer.³⁰ During the past 20 years, hundreds of cancer chemoprevention studies have been funded, including 70 randomized trials encompassing 130,000 subjects.³⁰ Large-scale clinical trials are in progress to identify the role of agents such as retinoids, tamoxifen, other selective estrogen receptor modulators (SERMS), finasteride, selenium, nonsteroidal anti-inflammatory drugs (including aspirin), and drugs that target RARB, ERB2, and EGFR in the prevention of several solid tumors.²⁹⁻³¹

Tamoxifen was the first chemoprevention agent approved by the US Food and Drug Administration (FDA) for breast

cancer.³² The National Surgical Adjuvant Breast and Bowel Project's Breast Cancer Prevention Trial (NSABP-P1) demonstrated that the use of tamoxifen in high-risk women reduced the risk of developing breast cancer by 49%. The benefit of tamoxifen in women at very high risk of breast cancer (eg, women with BRCA1 or BRCA2 mutations) has yet to be clearly demonstrated. Preliminary findings are now available about the effectiveness of tamoxifen as a chemopreventive agent in women who were participants in the NSABP-P1 and who also have a BRCA1 or a BRCA2 mutation.³³ The study demonstrated that in healthy women, younger than 35 years, tamoxifen reduced breast cancer incidence among BRCA2 carriers by 62%. In healthy women aged 35 years and older who are carriers of the BRCA1 mutation, tamoxifen did not reduce breast cancer incidence. The sample sizes of BRCA1 carriers (n = 8, 5 tamoxifen, 3 placebo) and BRCA2 carriers (n = 11, 3 tamoxifen, 8 placebo) were extremely low and the results did not reach statistical significance. New generations of selective estrogen receptor modulators, such as raloxifene, are being evaluated as chemopreventives in breast cancer.

Celecoxib, originally licensed as a treatment for arthritis, was recently approved by the US FDA as an adjunct to usual care for patients with FAP. This was based on the results of a double-blind placebo-controlled trial in 83 patients with FAP showing that Celecoxib twice daily for 6 months reduced the number of polyps by 28%.³⁴ One of the advantages of systemic chemopreventive agents such as Celecoxib is that they have the potential to reduce the risk of cancer in more than one organ system. In light of at least limited successes with Celecoxib, the National Cancer Institute is currently sponsoring clinical prevention trials of Celecoxib in a number of cancer types, including colon, esophagus, bladder, skin, prostate, and lung.³⁵

In the general population, it has been demonstrated that oral contraceptives reduce the risk of ovarian cancer by almost half after about 3 years of cumulative use.^{36,37} These studies found that the reduction in ovarian cancer persisted for at least 15 years after use ended and was independent of the specific type of medication formulation and histologic type of epithelial cancer.

In the population where women are at very high risk of ovarian cancer, eg, women with BRCA1 and BRCA2 mutations, there are limited and contradictory data regarding the use of oral contraceptives in preventing ovarian cancer. Although one study suggests that the oral contraceptives may reduce the risk of ovarian cancer in those carrying mutations, another study suggests that this hormone exposure may increase the risk of breast cancer in this same group.^{38,39} In addition, a recent population-based case-control study in which information was available regarding both BRCA genotype and oral contraceptive use failed to demonstrate a reduction in ovarian cancer risk.⁴⁰ These investigators conclude that it is premature to use oral contraceptives for the chemoprevention of ovarian cancer in BRCA mutation carriers. Encouraging women at high-risk with and without BRCA mutations to participate in longitudinal studies is critical to gather the data needed for evidence-based advice.

In addition, there is an emerging trend to do more sophisticated genetic analyses of potential modifying genes in those who carry germline mutations in genes such as BRCA1 and BRCA2. There are several examples that illustrate this trend. Currently, there are several reports of ovarian or breast cancer risk in BRCA1 or BRCA2 carriers that may be modified by the several genetic polymorphisms. Phelan and colleagues report that ovarian cancer risk in BRCA1 carriers that have 1 or 2 rare HRAS2 alleles have a higher rate of ovarian cancer (2.11 times greater) than BRCA1 carriers with only the common alleles.⁴¹ Furthermore, women bearing germline mutations falling within a region in the BRCA2 gene known as the ovarian cancer cluster region have a higher ovarian cancer risk than those with BRCA2 mutations outside this region.^{42,43}

More recently Levy-Lahad and colleagues reported that a single nucleotide polymorphism in the RAD51 gene did not affect ovarian cancer risk in BRCA1 or BRCA2 mutations carriers but that the RAD51-135C is a significant modifier of BRCA2 penetrance, specifically in raising breast cancer risk at younger ages.⁴⁴ Additionally, Wang and colleagues report that the single nucleotide polymorphism in the 5' untranslated region of RAD51 gene may be associated with an increased risk of breast cancer and a lower risk of ovarian cancer among BRCA2 mutation carriers.⁴⁵ The exact biochemical basis of the modification in risk has yet to be elucidated; however, the efficacy of any given chemoprevention strategy may need to be interpreted against the backdrop of the specific genotype of study participants.

■ Secondary Cancer Prevention in the General Population and in Genetic High-risk Populations

Secondary cancer prevention refers to the use of screening tests or examinations to detect cancer before it is clinically evident. This differs from *diagnostic* testing, which involves a systematic evaluation of existing signs or symptoms of a disease. Criteria for screening recommendations are currently based on age, family history, previous medical history of cancer, and other risk factors. The identification of individuals at increased cancer risk due to genetic susceptibility allows for the consideration of using screening tests and examinations at an earlier age than might be recommended for the general population. Ultimately, it may become possible to customize surveillance recommendations to an individual's profile of risk so that he or she can receive tailored screening, eg, female BRCA1 and BRCA2 mutation carriers are screened at younger ages and at more frequent intervals for both breast and ovarian cancer. Conversely, those individuals who come from high-risk families with a known deleterious mutation and who test negative for that familial mutation, can be spared the burden of increased cancer screening.

Recommendations for risk reduction and screening activities in high-risk families are beginning to appear in the literature. For some cancer susceptibility conditions with childhood

Table 1 • Options for Surveillance for Carriers of BRCA1 and BRCA2 Mutations^{17*}

Intervention	Provisional Recommendations
Breast self-examination	Education regarding monthly self-examination
Clinical breast examination	Annually or semiannually beginning at age 25-35 y
Breast mammography	Annually, beginning at age 25-35 y
Ovarian transvaginal ultrasound with color Doppler and CA-125	Annually or semiannually, beginning at age 25-35 y
Prostate cancer surveillance for men who carry BRCA1 mutations only	Inform regarding options for screening involving digital rectal examination, prostate-specific antigen blood test, annually beginning at age 50 y
Colon cancer surveillance	Follow American Cancer Society general population recommendations: eg, fecal occult blood test annually and flexible sigmoidoscopy every 3-5 y beginning at age 50 y

*Based on US Preventive Services Task Force criteria, level III evidence, ie, expert opinion and case reports only. These recommendations in most cases are of unproven benefit and have limited screening sensitivity, and there is insufficient data to determine the optimal age of beginning screening or the screening interval.

onset, such as VHL and MEN2, recommendations for primary and secondary prevention exist and the efficacy of these strategies is reasonably well documented.⁴⁶⁻⁴⁹ However, the surveillance recommendations for hereditary breast, ovarian, and colon cancer are still evolving. Although the exact age at which to begin screening is still being debated, women in the general population are advised to begin regular mammograms sometime during their 40s.^{21,50} In contrast, those at higher genetic risk are often urged to begin mammography at a younger age.¹⁷ Unfortunately, there are no data to prove that early initiation of mammographic screening in this setting is associated with the same down-staging and improved survival as has been demonstrated in postmenopausal women. Further, it is well known that the increased density of the breasts in young women severely compromises the sensitivity of mammographic screening. This has led to a major interest in alternative breast imaging modalities for women at increased genetic risk of breast cancer. Magnetic resonance imaging (MRI) of the breast appears to be a promising alternative in the high-risk setting,⁵¹ and the National Cancer Institute and the American College of Radiology Imaging Network (NCI/ACRIN) are launching a multicenter study to compare digital mammography to standard mammography for the detection of breast cancer (information available on the NCI/ACRIN study at <http://newscenter.cancer.gov>).

The International Collaborative Group for the Study of HNPCC (ICG-HNPCC) has published recommendations for screening in HNPCC families for persons at increased risk by either family history or genetic testing.⁵⁰ The National Institutes of Health and Department of Energy (NIH-DOE) Eth-

ical and Legal Social Implications (ELSI) Cancer Genetics Consortium has also issued recommendations regarding both BRCA1¹⁷ and HNPCC¹⁶ screening.²⁰ These guidelines are based primarily on expert opinion and will be updated in the future as more data becomes available (Tables 1 and 2).

■ Genes and the Development of Biologic Surrogate Endpoints

Previously, cancer prevention studies were restricted to outcomes that could be measured easily, eg, detection of new cancer, mortality from cancer, or clinically significant side effects from treatment. However, studies based on these endpoints typically must be very large and may take many years to complete. Technologies involving molecular genetics offer the promise of new tools that may allow assessment of biomarkers as intermediate study endpoints (or surrogate biomarkers) for risk assessment, early detection, chemoprevention, and second primary cancer prevention trials.^{52,53} Markers of risk and early disease must be part of the etiologic pathway that leads to the development of disease; however, they differ in the degree of certainty that they convey regarding the eventual progression to cancer. A risk factor generally confers a "disease susceptibility" that is increased relative to the general population but that is not usually 100%. Early detection markers indicate the presence of cancer or suggest that cancer will occur with nearly a 100% certainty within a specified time interval. For the marker to serve as a valid intermediate surrogate endpoint,⁵⁴ it must be:

Table 2 • Options for Surveillance for Carriers of HNPCC-associated Mutations^{16*}

Intervention	Provisional Recommendations
Colonoscopy	Begin at age 20-25 y, repeat every 1-3 y
Transvaginal ultrasound or endometrial aspirate	Annually beginning at age 25-35 y

*Based on US Preventive Services Task Force criteria, level III evidence, ie, expert opinion and case reports only. These recommendations in most cases are of unproven benefit and have limited screening sensitivity, and there is insufficient data to determine the optimal age of beginning screening or the screening interval.

- a determinant of outcome
- modulated by the pharmacologic agent
- demonstrate variations that correlate with variation in cancer incidence

An example of the research involved in the development of surrogate biomarkers is the work being done in colon cancer. A number of such markers are being evaluated for use in colon cancer, including APC mutations, MMR, K-ras, p53, various kinases, serum markers, L-DNA, B-catenin, bcl-2, cyclin D1 and E1, SMAD4, and panels combining many of the above markers.⁵⁴ Once surrogate biomarkers of biologic response and susceptibility have been adequately validated, it will be possible to select well-defined populations based on tumor characteristics and genetic susceptibility for prevention and chemoprevention trials.

The effectiveness of the chemopreventive agents may also be measured by molecular means. Toward this end, the NCI has established a multi-institutional consortium, the Early Detection Research Network (EDRN), to develop sensitive and specific tests for the earlier detection of cancer. The goal is to link investigators with various areas of expertise and to develop the research designs, technologies, and infrastructures to facilitate identification of molecular, genetic, and biologic markers for early cancer detection. For more information, see the EDRN website at <http://edrn.nci.nih.gov/index.html>.

■ Genetics in Cancer Diagnostics

Precise cancer diagnosis is essential to:

- understanding the pathophysiology of cancers
- offering an accurate prognosis
- establishing appropriate medical management
- developing more targeted methods of therapy

There may be several levels of diagnostic information that could be acquired from a given affected individual, including the clinical diagnosis of a specific malignancy, the genetic subtype of that malignancy, and the genetic diagnosis of an underlying cause for that malignancy. When cancer is suspected, further tests are undertaken to confirm the diagnosis. These may involve tests of blood, urine, body fluids, imaging modalities, or tissue biopsy.

An example of how genetics are used in the diagnostic setting is provided by the classification of acute leukemias. All diagnoses in acute leukemia are based on the morphologic classification and immunophenotypic classification of the hematopoietic cells in the bone marrow. Genetic evaluation further refines the diagnosis in most of the leukemias. For example, in acute promyelocytic leukemia (APL) there is a translocation between chromosome 15 and 17 [t(15;17)].⁵⁵ This genetic information pinpoints the diagnosis and identifies a group of patients with APL that respond to treatment with all-trans retinoic acid and arsenic trioxide.^{56,57}

The recognition of the specific underlying genetic condition will have an impact on the medical management of individual patients.⁵⁸ The clinical diagnosis of pheochromocytoma is established through biochemical testing, imaging, surgical exploration, and histopathologic examination. Although most

pheochromocytomas are sporadic events, a subset occur as a consequence of inherited cancer susceptibility in such diverse disorders as VHL disease, MEN, type 2, hereditary paragangliomas, and neurofibromatosis, type 1. Each of these has a different genetic basis, involves different organs, and has different natural histories.

By identifying an underlying genetic condition, patient management can be tailored to maximize the benefit of treatment.

■ Genetics Cancer Prognosis

A large number of genetic and phenotypic changes have been suggested as markers of prognosis in various types of solid and hematologic cancers. Though many are currently being evaluated for use in improving cancer prognosis, only a few have been fully characterized and developed to the point where they influence clinical care. A prognostic marker is defined as any measurement available at the time of diagnosis or surgery that is associated with disease-free or overall survival.^{59,60} Traditional prognostic markers for cancer survival include age, ethnicity, tumor stage, size, hormone responsiveness, histologic subtypes, lymph node status, and various other biomarkers. A few examples of current cancer prognosis research are presented to illustrate how molecular genetic analysis of human tumors (including characterization of proliferation, oncogenes, tumor suppressor genes, and other proteins) affects our understanding of cancer prognosis.

Immunohistochemistry (IHC) targets specific gene products or mutation analysis of specific oncogenes can provide prognostic information in a variety of cancer types. For example, it has been found that an oncogene known as HER-2/neu is amplified in approximately 20% to 30% of breast and ovarian tumors and that this oncogene's amplification and/or overexpression is a reliable indicator of poor prognosis.^{61,62} Thus, the HER-2 assays may be useful for differentiating patients at higher risk of cancer recurrence as well as identifying a subset of patients who are more likely to have a poor response to adjuvant hormonal therapy (tamoxifen) or chemotherapy (5-FU, methotrexate, and cyclophosphamide [Cytoxan]).⁶³⁻⁶⁵ This observation has also led to clinical research trials investigating HER-2/neu monoclonal antibodies with chemotherapy to target specifically the cancer cells overexpressing HER-2/neu, which is discussed in the treatment section.

A specialized DNA microarray, the "Lymphochip," was developed by Alizadeh and colleagues to permit characterizing the pattern of gene expression in lymphoproliferative neoplasms.⁶⁶ Recent data show that it is possible to subclassify diffuse large B-cell lymphomas (DLBCLs) into 2 molecularly distinct groups: germinal-center B-like tumors and activated peripheral B-like cell neoplasms. Individuals with germinal-center B-like tumors DLBCLs have a prolonged overall survival when compared with the individuals with activated peripheral B-like DLBCL neoplasms. The former respond very well to conventional anthracycline-based lymphoma treatment regimens, whereas the latter group does not. This information could, therefore, be used to select previously untreated DLBCL patients for whom upfront investigational therapy represents a more logical treatment strategy.

Tumor suppressor genes are frequently mutated or deleted in cancer patients. These changes generally occur at the somatic level, ie, they are not heritable. Of these, the p53 gene is the most commonly mutated, with somatic mutations found in at least half of all types of cancer. Multiple studies have shown that p53 is an independent marker of prognosis in breast cancer and in other tumors.⁶⁷ Abnormal p53 protein expression is associated with decreased survival. In breast cancer, the predictive usefulness of p53 status is further enhanced when combined with other prognostic indicators such as family history and lymph node status.⁶⁸⁻⁷⁰

Research continues to assess other genetic factors that serve as prognostic factors.

In the case of colorectal cancer, the presence of microsatellite instability (MSI) may have implications for etiology, prognosis, and treatment. MSI results from either inherited (HNPCC) or acquired (sporadic) mutations of DNA mismatch-repair genes (eg, MLH1, MSH2, or MSH6). MSI may be present in half the colorectal cancers in children and young adults, and only one third of patients with colon cancer and MSI present in the tumor have a family history of colon cancer.^{71,72} When compared with stage-matched low-frequency microsatellite instability (MIS-L) and stage-matched microsatellite instability stable (MSS) tumors, the presence of high-frequency microsatellite instability (MSI-H) in the tumor has been shown to be associated with:

- tumors predominantly in the proximal colon
- a less aggressive clinical course
- greater sensitivity to antimetabolites
- improved survival

These findings suggest that by testing for microsatellite instability, and possibly other genetic alterations (eg, allelic loss, p53, and others), it may be possible to define groups of patients with different prognosis and survival and who require different adjuvant therapies.^{73,74}

Experimental markers on the horizon of clinical care will attempt to define the molecular bases of the processes involved in treatment failure, including invasion, angiogenesis, metastasis, and resistance to therapy.⁵⁹ Scientists predict that panels of molecular prognostic markers in cancer will be developed from the application of new molecular biology tools to cancer tissue. These new tools include laser captured microdissection (LCM), fluorescence in situ hybridization (FISH), complementary DNA (cDNA) chip array methods, SAGE (serial analysis of gene expression). As molecular markers based on the individual patient's tumor biology replace more generic prognostic indicators, the accuracy of patient diagnosis, prognosis, and prediction of response will improve. This will lead to the discovery of new targets for more biologic-based therapies and prevention strategies for cancer.

■ Genetics in Monitoring for Minimal Residual Disease

Recurrences of cancer are often caused by small amounts of clinically undetectable cancerous tissue remaining in the body after surgery or treatment. This is called "minimal residual disease" (MRD). It is hypothesized that improving our ability to

detect MRD offers an opportunity to refine and enhance patient treatment decisions. The value of molecular genetics techniques is their use in detection of residual disease in situations that appear normal by other criteria such as histopathology or radiographic studies.

The management of APL provides a good example of how genetic information is used in the monitoring for minimal residual disease. The presence of the PML (promyelocytic leukemia)/RAR α (retinoic acid receptor alpha) fusion gene, as detected by reverse transcriptase polymerase chain reaction (RT-PCR), may predict relapse in patients with APL who are in a hematologic complete response (CR). This information identifies individuals who may benefit from aggressive treatment and those who do not appear to benefit.⁶⁰ The 15;17 translocation in APL provides the critical connection between improvements in diagnosis and monitoring for MRD, leading to improvements in treatment. The 15;17 translocation results in disruption of the RAR α gene on chromosome 17 and of the PML gene on chromosome 15. Normal RAR α function is needed for stem cell differentiation and maturation. Without it, there is cell arrest at the level of the promyelocyte, and APL develops. Standard therapy for APL now consists of chemotherapy and all-*trans*-retinoic acid (ATRA), which produces a complete response (CR) in approximately 90% of patients. Despite excellent response rates, 30% of patients relapse. In those patients able to achieve a second hematologic CR, autologous bone marrow transplant (ABMT) has been reported to offer a chance for cure.⁶¹ For the patients who were in a hematologic CR as well as RT-PCR negative (molecular CR) for the PML/RAR α fusion gene before ABMT ($n = 8$), 75% were in a hematologic and molecular CR, with median follow-up of 28 months. For the patients who were in a hematologic CR but were not in a molecular CR (RT-PCR positive) before ABMT ($n = 7$), all remained positive during follow-up for ABMT and relapsed at a median time of 5 months from ABMT. Thus, information regarding the presence or absence of MRD can be used to stratify those patients who may benefit from aggressive therapy and those who may not.

■ Genetics in Cancer Treatment

Rational drug therapy, also referred to as targeted gene products or molecular targeted therapy, consists of individually tailored treatment interventions based on the molecular characteristics of the malignancy.⁵⁹ This approach exploits the distinctive features of the malignant phenotype, which include rapid and unlimited growth, invasiveness, metastatic potential, and the ability to produce angiogenesis, as contrasted with the phenotype of normal cells.^{75,76} Drugs that target the molecular differences between tumor and normal cells—the altered genes or protein products or corrupted pathways—hold the possibility of being more effective and less toxic than standard cancer treatments.

The treatment of APL with ATRA is a good example of molecular-targeted therapy.⁷⁷ This treatment targets the novel genetic lesion created by a disease-specific chromosomal translocation, which alters the RAR α gene. Disruption of the RAR α gene, or blocking its response element by any one of

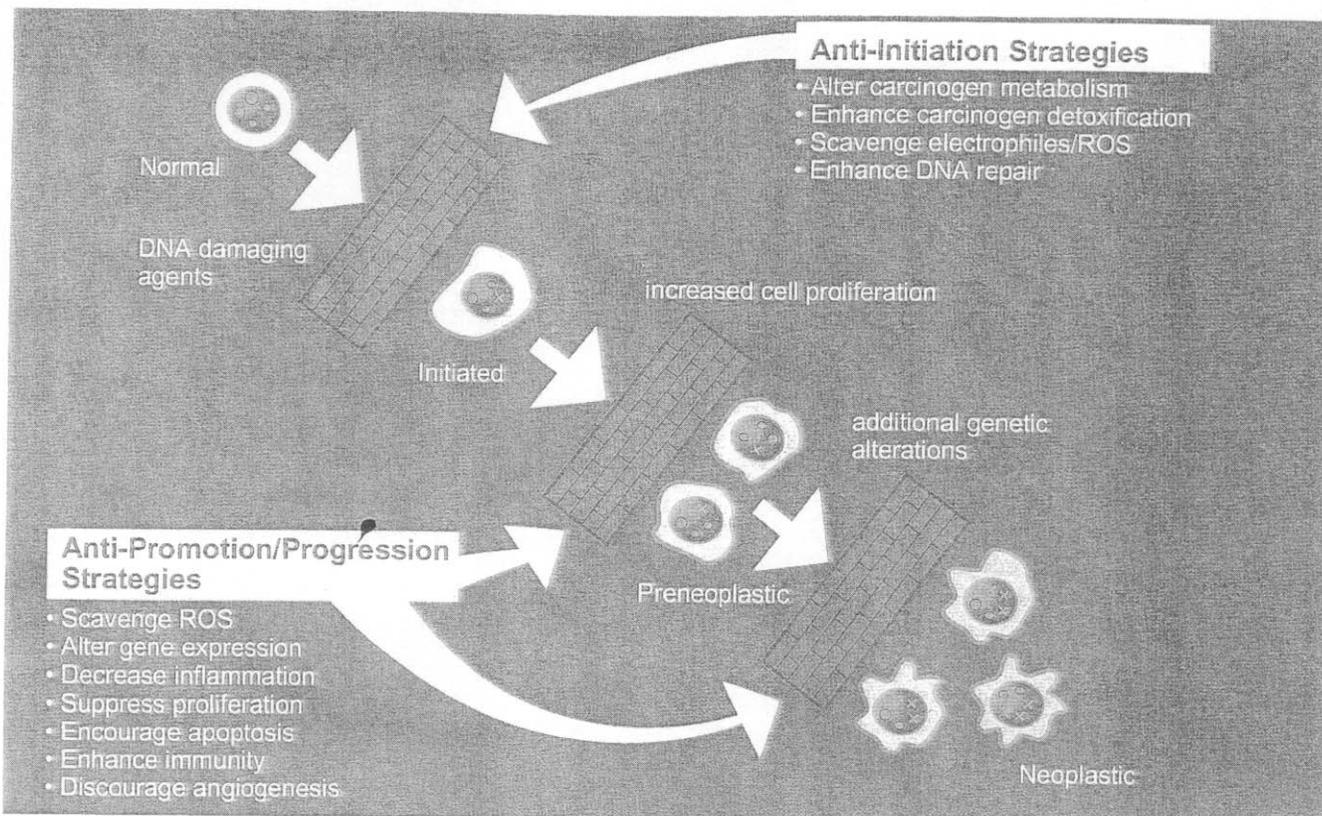


Figure 2. Gleevec represents the first approved drug to directly turn off the signal of a protein known to cause cancer.

several possible translocations, leads to a reduction in the functional amount of its product. Standard treatment now consists of replacing RAR α with the medication, ATRA. ATRA appears to reverse the arrest in the maturation of malignant promyelocytes, created by APL's pathogenic 15;17 chromosomal translocation, allowing them to undergo normal maturation and death. ATRA plus chemotherapy is now standard in the treatment of APL, and patients who receive maintenance in the form of either chemotherapy or intermittent ATRA have superior survival.⁷⁷ Thus, cytogenetic studies lead not only to rational drug therapy but also to increasingly accurate predictions of biologic response based on the underlying genetic basis of the disease.

Another approach is to increase the specificity in targeting genes or gene products of cancer cells with biologic therapies. Trastuzumab is a monoclonal antibody that targets the protein product of the HER2neu gene. The HER2 (or *c-erbB2*) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. HER2 protein overexpression is observed in 25% to 30% of primary breast cancers. HER2 protein overexpression can be determined using an immunohistochemistry-based assessment of fixed tumor blocks. Trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.⁷⁸⁻⁸⁰ Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC).^{82,83} In vitro, HERCEPTIN-mediated ADCC is preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.⁸³ It has

been approved by the FDA as an effective single-agent treatment for metastatic breast cancer. Median overall survival rate of 13 months in patients with metastatic breast cancer is superior to results reported for second-line chemotherapy in metastatic breast cancer.⁸⁴ It also potentiates the antitumor effect of paclitaxel (Taxol) chemotherapy by 25% to 57%.⁸⁵

CML is a clonal hematopoietic stem-cell disorder characterized by the (9:22) translocation, also known as the Philadelphia chromosome.⁷⁶ The translocation involves the *abl* segment from chromosome 9 being translocated to chromosome 22 and the *bcr* portion of chromosome 22 being translocated to chromosome 9. This results in the production of an activated *bcr-abl* tyrosine kinase, resulting in marked myeloid proliferation, which terminates in an acute leukemia. Conventional therapy includes interferon-based regimens, stem-cell transplantation (SCT being the only curative therapy), and now STI571. Recently, the FDA approved imatinib (STI571 or Gleevec) for the treatment CML and gastrointestinal stromal tumors (GIST). Gleevec represents the first approved drug to directly turn off the signal of a protein known to cause cancer (Figure 2). Gleevec is a potent inhibitor of the Bcr-Abl tyrosine kinase, which is present 95% of patients with CML and is absolutely required for the transforming function of the Bcr-Abl protein.⁸⁶ In addition, Gleevec also is a potent inhibitor of the *c-Kit* tyrosine kinases,⁸⁷ hence its activity in the two specific cancers cited. Data from phase I and II trials in CML patients demonstrated a 98% hematologic response rate.⁸⁸⁻⁹¹ Phase II trials in gastrointestinal stromal tumors has show that STI571 is well tolerated and has impressive clinical activity in a disease that is unresponsive to standard chemotherapy.^{92,93}

Novel, gene-based treatment strategies that are currently being tested include the use of ribozymes, growth factor receptor antibodies, immunotoxins, oncotoxins, neutralizing antibodies, inhibitory ligands and agents that interfere with growth factor action, signal transduction, invasion, metastasis, and angiogenesis. Although most of these treatments are in preclinical development or just entering early clinical trials, the trend toward increasing specificity of treatment modalities is expected to continue to find its way into clinical practice.

One final impact of genetic technologies on cancer treatment deserves discussion: that of treatment decisions for persons with inherited susceptibility to cancer. Those carrying mutations in cancer susceptibility genes have unusually high risks of developing more than one primary malignancy.¹⁹ Breast cancer patients who have an inherited form of breast cancer, for example, the risk/benefit calculation involved in choosing between mastectomy and lumpectomy plus radiation will be influenced by knowing that a particular patient has a 60% chance of developing a second breast cancer or by recalling that ATM homozygotes have a genetic sensitivity to the carcinogenic effects of ionizing radiation.²⁴ In colon cancer treatment, bowel-conserving surgery at diagnosis of a carcinoma or dysplastic adenomatous polyp may not be in the person's best interest if this occurs in persons with FAP or HNPCC, in whom the likelihood of subsequent colon malignancies is high.²⁰ Therefore, the treatment strategy selected in such a persons may differ from that recommended for an individual without a genetic predisposition.

■ Gene Therapy

Future options for cancer treatment will undoubtedly involve gene therapy, which can be defined as the introduction of new genetic material into cells with therapeutic intent. Thus, the goal of gene therapy is to correct a gene mutation or alteration in a cell to prevent, treat, or cure a disease that is caused by a malfunctioning gene. Gene transfer requires that functional exogenous genes, called transgenes, be transferred efficiently into affected cells.²⁵ However, it is unlikely that gene therapy alone will result in a significant clinical impact in the treatment of most existing tumors any more than any single chemotherapeutic agent is likely to be effective.²⁶ In most of the common solid tumors, there are multiple, perhaps hundreds of gene defects within each tumor, and the technical feasibility of repairing or replacing multiple genes would be very complex.

Various gene therapy strategies are under development, which include: (1) germline gene transfer in which the gene correction is made to the egg or sperm cells to prevent future inherited illnesses and (2) somatic cell gene therapy, in which nonreproductive organs are targeted. Germline gene transfer has substantial ethical implications regarding the possibility of misuse, such as eugenic applications intended to remove undesirable traits from the human gene pool or nondisease related genetic enhancements intended to improve desirable traits, such as intelligence, athletic ability, hair or eye color. To prevent such inappropriate applications the ethical implications of genetic technologies applications must always be carefully considered.

Somatic cell gene therapy for the transfer of corrected, or altered genes, into human cells, is the only form of gene therapy that has been approved for clinical trials. Most clinical cancer genetic research trials are currently focused on investigating diagnostics and repair or replacement of defective genes and have been conducted primarily to assess the toxicity and tolerability of the gene therapy. These corrected or altered genes can be delivered to the body through two approaches. The *ex vivo* route takes the cell of interest from the patient, corrects the genetic defect in these cells while in an external lab setting, and then returns them back to the patient. Direct gene transfer *in vivo* involves introducing a corrected gene directly into target cells in the body. Both approaches require a vector to carry the new genetic information into the host cell. Examples of biologic vectors include retroviruses, adenoviruses, and plasmids. Nonviral methods of gene transfer, such as chemical transfer, liposomes, and direct microinjection of DNA, RNA, or their protein products, are also under investigation.

Cancer accounts for the majority of gene therapy trials being carried out worldwide. Current gene therapy studies for cancer have been reviewed in recent publications.²⁶ The therapeutic approaches for cancer gene therapy approved by the National Institutes of Health Recombinant DNA Advisory Committee (NIH RAC) are summarized in Table 3. These studies include marker gene protocols that use genemarked cells to track outcomes of introduced gene therapy cells or other cells of interest. Other protocols are designed to assess the effectiveness and safety of genes that target genetic alterations thought to cause cancer, such as the p53 gene. To date, there are a number of significant barriers to effective cancer gene therapy that have prevented its widespread application to cancer care. These include limited technical ability to transfer and express new genes in target cells, the lack of vector specificity, limited antitumor effect of the transgene, and the inability to target every tumor cell.²⁷ Especially vexing are barriers to the development of successful vectors for delivery of the gene therapies to target cells other than bone marrow. Although gene therapy approaches to tumor immunotherapy are showing some promise, they are still in their infancy.

Until recently, there was little evidence of efficacy that might justify the enrollment of patients in large randomized phase III clinical trials of gene therapy. However, recent suggestions of clinical activity in patients receiving intratumoral or intraperitoneal injections of gene therapy vectors have led, finally, to the initiation of phase III trials in head and neck cancer and in ovarian cancer.²⁷

■ Conclusion: The Nurse's Role

The translation of genetic research into clinical practice has medical, social, ethical, and legal implications on many levels, including individual, familial, and societal.²⁸ Nowhere is this more evident than in cancer genetics. The oncology nurse has an important role in ensuring the safety of those involved in

genetic studies. Nurses practicing in either clinical or academic roles have the opportunity to become involved in patient care activities related to:

- providing education to the patient and family regarding how genetic tests are done
- assessing the outcomes of individual and family decisions related to genetic information
- monitoring how therapies are administered
- assessing potential toxicities of treatment
- helping patients and families understand other issues related to applying cancer genetics to patient care
- participating in the design and integration of safe applications of genetic technologies
- developing optimal methods of applying genetic technologies to cancer risk-reduction surveillance, diagnosis, and treatment

The involvement of professional nurses at each phase of clinical practice and research will enhance patient outcomes and contribute to the ever-evolving literature in cancer genetics.

Several nursing professional organizations have developed position statements regarding the importance of integrating genetics tools and strategies into all nurses' professional practice. The International Society of Nurses in Genetics (ISONG), the Oncology Nursing Society (ONS), and the American Nurses Association (ANA) have set standards for and defined the scope of professional nursing practice in genetics.^{99,100} Information regarding the scope of practice in genetics is available on their Web sites:

- ISONG—<http://nursing.creighton.edu/isong>
- ANA—<http://www.nursingworld.org>
- ONS—<http://www.ons.org>

The ONS believes that general and advanced practice nurses in oncology must have a foundation of genetic knowledge. Nurses are expected to be resources to patients, their families, and the public regarding the implications of genetics cancer education, prevention, early detection, and psychosocial support in all phases of cancer care.

An advanced practice credential in genetics that may be of interest to advanced practice nurses and particularly those in oncology is now available through ISONG. ISONG has recently developed a credential for the Advanced Practice Nurse in Genetics, APNG (c). Information regarding the requirements for the ISONG certification is available at its Web site previously mentioned.

Oncology nurses have begun to integrate knowledge of genetic technologies into all phases of care for patients with cancer and their families. The information is applicable for those considering genetic testing, those with a notable family history of cancer, and those with known carcinogen exposures that put them at risk of cancer. Learning how to screen and manage high-risk patients through the use of new or better genetic technologies poses significant challenges to all healthcare providers. A list of professionals providing cancer genetics services is available at <http://cancer-net.nci.nih.gov/genesrch.shtml>. Information regarding referral into clinical trials can be obtained through the NCI Web site: <http://www.cancertrials.nci.nih.gov> or by calling the NCI Cancer

Table 3 • Cancer Gene Therapy Trials Approved by the NIH Recombinant DNA Advisory Committee

Cancer (by Therapeutic Approach)	No. of Clinical Trials
Antisense	7
Chemoprotection	10
Immunotherapy/in vitro transduction	72
Immunotherapy/in vivo transduction	77
Prodrug/HSVTK and ganciclovir	34
Tumor-suppressor gene	27
Single-chain antibody	2
Oncogene down regulation	4
Vector-directed cell lysis	4
Total	237

From the National Institutes of Health Office of Biotechnology Activities at <http://www4od.nih.gov/oba>.

Information Service at 800-4-CANCER. The American Cancer Society (ACS) information line (800-ACS-2345) and Web site (<http://www.cancer.org>) has patient and professional information available with links to many other cancer-related Web sites. The ACS also has cancer information specialists available at its regional offices throughout the country to assist practicing nurses in answering patient questions related to cancer care.

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