

Programmed Instruction: Cancer Genetics

Clinical Applications of Genetic Technologies to Cancer Care

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INTRODUCTION

This is the fifth in a series of six self-learning modules that review the role of genetics in oncology and the implications of this information and technology on the practice of oncology nursing. As oncology nurses study this module, they will become familiar with how new genetic technologies are being incorporated into clinical oncology practice. Specifically, the knowledge of cancer genetics discussed in earlier modules is applied to cancer risk reduction, screening, diagnosis, prognosis, monitoring for residual disease, treatment, and gene therapy.

OBJECTIVES

After completing this self-learning module, the nurse will be able to do the following:

- Describe the impact of understanding molecular carcinogenesis on cancer management.
- Discuss the genetic basis for differences in cancer risk due to carcinogen exposure.
- Describe risk-reduction and screening recommendations for persons with inherited breast-ovarian and colon cancer susceptibility syndromes.
- Describe the current and potential utilization of genetic knowledge in cancer diagnosis, prognosis and treatment.

This self-learning module has three components:

- Pretest.
- Content, with questions and answers.
- Posttest.

INSTRUCTIONS

The instructions are as follows:

- Complete the pretest.
- Read each content section and answer the questions after each section.
- Complete the posttest after reading the self-learning module.

This module will take approximately 1 to 2 hours to complete, but can be completed at one's own pace.

The answers to the pretest and content questions are located at the end of the module.

This module meets the requirement of the Board of Nursing, State of Florida, for Continuing Education Nurs-

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PRETEST

TRUE OR FALSE:

- _____ 1. One strategy for cancer risk reduction is avoidance of known carcinogens.
- _____ 2. Chemoprevention for colon cancer is being tested in clinical trials.
- _____ 3. Aspirin is used for chemoprevention of colon cancer.
- _____ 4. Chemoprevention clinical trials always give the patient a medication.
- _____ 5. Chemoprevention is used only for precancerous conditions.
- _____ 6. Biomarkers are used to treat patients with cancer.
- _____ 7. The immune system of an individual may contribute to susceptibility to cancer.
- _____ 8. Surgery is one method of cancer risk reduction currently being used.
- _____ 9. Gender is used as a criteria to determine cancer screening of individuals.
- _____ 10. The diagnostic workup of leukemias often incorporates genetic testing.
- _____ 11. Assessment of oncogenes assists in determining cancer prognosis currently.
- _____ 12. Gene therapy often involves administration of a virus.
- _____ 13. Gene therapy involves only in vivo methods.
- _____ 14. Nurses are involved in the monitoring of patients' responsiveness and the outcomes of gene therapy.
- _____ 15. Genetic methods can be used to monitor residual disease.

BACKGROUND

Increased understanding of the molecular biology and genetic bases of cancer susceptibility, initiation, promotion, progression, invasion, and metastases will enable the nurse to apply this knowledge to cancer care. Genetic discoveries are coming at an increasing pace, due largely to the Human Genome Project (HGP), a 15-year project that began in 1990 to map and identify the full set of genetic instructions in humans and other model organisms (1). In fact, genetic advances generated by the HGP are already beginning to affect every phase of cancer care (Table 1) (2). It is hoped that the understanding of cancer

TABLE 1. Selected applications of genetic advances to oncology care

<i>Prevention</i>	Utilize genetic heterogeneity in carcinogen metabolism
<i>Diagnosis</i>	Recognition of leukemia-specific translocations
<i>Prognosis</i>	Evaluation of oncogene and tumor suppressor mutations
<i>Treatment modalities</i>	Rational drug choices and targeted gene therapies
<i>Treatment monitoring</i>	Molecular evaluation of surgical margins and metastasis sites
<i>Genetic susceptibility</i>	Identification of high risk individuals through genetic susceptibility testing

at the cellular level will improve cancer management by allowing for the following:

- A biologically relevant basis for understanding the fundamental causes of different cancer types.
- Selection of well-defined populations for risk reduction, early diagnostics, and clinical treatment trials.
- Increased accuracy and specificity of diagnosis, surveillance, treatment, and prognosis information.
- Modification of standard risk-reduction, medical surveillance, and treatment options for those with genetic susceptibility to cancer on the basis of genetic susceptibility testing.
- Development of gene therapies and individually tailored drug therapies with specific molecular targets.

1. List five areas of cancer management that will be improved by genetic advances:
 - a. _____
 - b. _____
 - c. _____
 - d. _____
 - e. _____

GENETIC ASSESSMENT OF CANCER

Recent biomedical discoveries make it clear that some clinical manifestations of many common diseases, including cancer, can be traced to specific genetic alterations (3). Cancer involves the progressive disruption of the genetic material in malignant cells in the target organ (4). This process is often broken into stages of initiation, promotion, and progression. The genetic disruption may be on the microscopic level of chromosomal aberrations or on the molecular level of gene mutations. Most of these alterations are somatic, that is, occurring only in cells in the target organ (e.g., genetic alterations of hematopoietic stem cells resulting in leukemias). Some genetic alterations are inherited, occur in every cell of the body including the

germ cells in the gonads, and thus can be passed on to future generations (5). These are known as mutations in cancer susceptibility genes. This module concentrates largely on somatic changes that can be detected through molecular biologic methods, except where noted.

The ability to detect genetic changes is growing rapidly and will have a major impact on cancer care. Some of these newer techniques allow greater specificity in determining exactly what genetic material is involved in the carcinogenesis of a particular malignancy. This capability of determining specific genetic changes present in various cancers is expected to enter clinical practice in the foreseeable future once cost and technical obstacles are overcome.

Detection of small genetic alterations in DNA material such as missense, nonsense, and frameshift mutations requires a variety of molecular methods because they are too small to be seen with common cytogenetic studies. Thanks to modifications of the polymerase chain reaction (PCR), first introduced in the early 1980s, these tests can be done on very small tissue samples, theoretically as small as a single cell. Other innovative methods combining molecular and cytogenetic techniques of genetic analysis are being developed in both research and clinical laboratories and may eventually become standard care. Other trends in genetic analysis are miniaturization, automation, and computerization of many tedious, repetitive steps in the molecular analysis process, so that many tests can be run simultaneously in shorter times and smaller spaces with fewer technical personnel.

For detection of genetic mutations, the current standard for genetic testing is to obtain the full gene sequencing. However, this is costly, time intensive, can miss defects in gene regulation and gene expression, and may not be ideal for all situations. Until new technology is widely available for rapid and cost-effective sequencing, a current interim strategy is development of rapid preliminary screening methods to detect, quickly and rather inexpensively, the most commonly described mutations in a given gene before or instead of full genetic sequencing (6). Each of these genetic mutation screening techniques will detect some types of genetic alterations and miss others. The choice of method often is based on the size of the coding region of the gene to be scanned and on the complexity of its structure. Use of these techniques in clinical care will move cancer care forward by offering more precise molecular diagnosis to complement clinical findings. Oncology nurses will need continuing education to develop and maintain familiarity with evolving panels of testing methods being offered for evaluation of genetic changes in particular genes associated with specific cancers.

Another way that molecular technology will inform cancer care is through the efforts of the Cancer Genome Anatomy Project (CGAP) of the National Cancer Institute (NCI) of the National Institutes of Health (NIH). The overall goal of the CGAP is to achieve a comprehensive molecular characterization of normal, precancerous, and malignant cells. Like the HGP, the CGAP is designed to build an infrastructure of resources, information, and technologies that will provide a platform for the ultimate success of this program. The first two goals are (a) to establish an index of all genes expressed in selected types of tumors and (b) to support the development and dissemination of new technologies that allow high throughput analysis of gene and protein expression as well as mutation detection (7).

2. What three techniques in genetic testing are being tested and improved for detecting genetic mutations?
 - a. _____
 - b. _____
 - c. _____
3. What is the standard for detection of genetic mutations?

4. What is a goal of the Cancer Genome Anatomy Project?

GENETICS IN CANCER RISK REDUCTION

Another area that will be impacted by genetics knowledge is cancer risk reduction, also known as cancer prevention, a term we deliberately avoided on the advice several cancer activists who pointed out that true prevention of cancer is rare. Everyone has a statistical risk of developing some type of cancer. Although true cancer prevention is our ultimate goal, the current reality is that we can aim only to lower our statistical risk, to forestall the development of a clinically significant malignancy, or to decrease mortality through early detection. Thus, we call this section risk reduction rather than cancer prevention.

There are two basic risk-reduction strategies. The first is avoidance of factors known to be carcinogenic. These may be personal exposures (e.g., by smoking) or society-wide exposures (e.g., to air, water, soil, and food pollution). Generally, exposures generated by society as a whole are not addressed in the medical setting as often as in the policy and political arenas.

The second major risk-reduction strategy is to thwart the biologic onset of cancer through altered lifestyle, chemoprevention, or surgical prophylaxis. Increasingly, strategies for reducing risk for development of invasive or metastatic cancer utilize knowledge of molecular carcinogenesis to

alter, halt, or reverse advances along the carcinogenic pathways. Long latency periods between carcinogenic exposure and disease probably exist for many common cancers of late adulthood, for example, skin damage due to sun exposure in early life leading to later skin cancers, or the exposure of colonic epithelium to a variety of dietary carcinogens over a lifetime leading to colon polyps or colorectal cancer. Multiple factors can enhance or inhibit these processes of carcinogenesis. Colon cancer provides a classic example of a long carcinogenic process with well-defined stages that may be reversible or at least treatable before a life-threatening situation develops. More specifically, the process of developing colorectal cancer from normal mucosa is generally accepted as a long, multistep, multistage process proceeding from hyperproliferation of colonic epithelia to adenoma (polyp) formation, adenoma growth and increasing dysplasia, and possible invasive malignancy, with or without metastases. This long natural history affords opportunities for early detection and risk-reduction interventions such as chemoprevention.

5. What are two basic risk-reduction strategies for cancer?
 - a. _____
 - b. _____
6. What process occurs with colon cancer that affords opportunities for early detection and risk-reduction interventions such as chemoprevention?

CHEMOPREVENTION

Chemoprevention lies at the intersection of disease management and health promotion. The term "chemoprevention" for several decades has referred 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 (8). This field is dependent on an understanding of the factors that influence molecular changes involved in cancer initiation, promotion, and progression so that new agents can be used to block these transitions before the emergence of an invasive or clinically detectable cancer. Nationally, hundreds of laboratory research studies are investigating potential new agents. In 1995, NCI alone sponsored more than 50 ongoing clinical trials of 25 new compounds (9). Large-scale clinical trials are in progress to identify the role of agents such as retinoids, tamoxifen, finasteride, and aspirin in cancer prevention (10).

The most studied chemopreventive agents are the retinoids, which appear to influence cell differentiation

and proliferation by binding to receptor proteins in the nucleus of cells and thereby triggering a cascade of molecular events. Retinoids have been useful in treating oral leukoplakia and squamous cell carcinoma of the head and neck (10). Leukoplakia is thick white patches or plaque found on the tongue or gums. When present, these patches indicate a higher risk for progression to cancer of the head and neck. Retinoids have also been utilized to treat nonmelanoma skin cancers, but clinical results have been variable.

Tamoxifen is a nonsteroidal oral antiestrogen used in the treatment of breast cancer. There are now trials in progress to determine its use as a chemopreventive agent for breast cancer (11). The largest of these is a multicenter, prospective, randomized, controlled trial called the Breast Cancer Prevention Trial (BCPT) comparing tamoxifen to placebo. The BCPT is being coordinated by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and has accrued 13,000 women who will be followed for 5 years.

Finasteride is an inhibitor of an enzyme in the testosterone metabolic pathway. It is hypothesized that blocking the conversion of testosterone to its active form will decrease the androgenic stimulation of the prostate gland with minimal side effects. Like the BCPT, the Prostate Cancer Prevention Trial (PCPT) is an ongoing double-blind, randomized, placebo-controlled, multicenter trial of a potential chemopreventive agent selected because of knowledge of the hormonal influence on certain cancers. The PCPT is designed to assess whether finasteride can decrease the incidence of prostate cancer in men age 55 years or older with a family history of prostate cancer or in men of African American descent (12).

Primary risk-reduction strategies proposed for colon cancer include decreasing excessive fat and caloric intake and body weight, as well as increasing dietary fiber intake, calcium supplements, and aspirin treatments. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been extensively studied as potential agents for diminishing the incidence of colorectal cancer. A recent review (13) documented strong evidence that NSAIDs do decrease cancerous growths in the colon. Although the exact mechanism of action is not known, there is some evidence that aspirin interferes with prostaglandin synthesis and cell proliferation and may therefore disrupt the initiation and promotion stages of carcinogenesis. An NCI-funded Colorectal Adenoma Chemoprevention Study using Aspirin (CAPS) was begun in 1993 to determine whether 3 years of daily aspirin use will decrease the number and size of adenomas and increase disease-free survival in patients with a personal history of colorectal cancer.

In conducting chemoprevention clinical trials, a number of ethical issues must be faced. As outlined by Vogel and Parker (14), these issues include the enrollment of healthy individuals rather than cancer patients, confidentiality in recruitment, the enrollment of high-risk subjects, randomization to placebo arms that may offer no benefit to the individual, provision of adequate informed consent, trial monitoring, possible conflicts of interest between researchers and participants, and competing outcomes and toxicities.

Current and previous cancer prevention studies were restricted to outcomes that could be measured easily (e.g., clinically apparent cancer incidence or mortality and clinically significant side effects). It would be preferable to know the effectiveness of a particular risk-reduction strategy by analyzing biomarkers of cellular changes, without waiting for full-blown clinical malignancy to develop. Molecular genetics is now giving researchers new tools that make it possible to assess intermediate (e.g., somewhere in the carcinogenic process but before the development of clinically detectable cancer) biomarkers that indicate progression along the carcinogenic pathway. Once some of the many possible biomarkers of biologic response and susceptibility have been adequately validated, it will be possible to select well-defined intervention populations on the basis of tumor characteristics and genetic susceptibility for chemoprevention trials, the effectiveness of which can also be measured by molecular means (15).

7. What is chemoprevention?

8. Name four agents currently used in chemoprevention clinical trials?
 - a. _____
 - b. _____
 - c. _____
 - d. _____
9. What are eight ethical issues surrounding chemoprevention clinical trials?
 - a. _____
 - b. _____
 - c. _____
 - d. _____
 - e. _____
 - f. _____
 - g. _____
 - h. _____
10. In what way could molecular genetic research help define populations for chemoprevention clinical trials?

THE IMPACT OF INDIVIDUAL GENOTYPES ON MODERATELY INCREASED CANCER SUSCEPTIBILITY

People are not all alike genetically when it comes to cancer susceptibility. Certain individuals are more susceptible than others to certain cancers or to cancer in general. Two people exposed to the same agent might have very different biologic risks for cancer and therefore may react differently to the exposure and to risk-reduction methods. This is known as individual susceptibility and can involve the following factors: differences in metabolism of carcinogenic uptake, activation, and detoxification; DNA repair variations; inherited or acquired mutations in specific proto-oncogenes or tumor-suppressor genes; nutritional status; hormonal and immunologic factors.

One factor that differentiates members of the general population who differ in their susceptibility to cancer is genetic variations in carcinogen metabolism. Although some risk factors, such as radiation and selected carcinogens, can act directly to damage DNA, many carcinogenic substances require metabolic activation from a precarcinogen to an active carcinogen in order 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 efficiency of these enzymes, which in turn leads to variability in cancer susceptibility. Other enzyme systems are involved in the detoxification of carcinogens already activated, and these too vary in efficiency and speed. There are also genetic variations in the cellular mechanisms that repair DNA damaged directly by certain carcinogens. Combinations of these different mechanisms of carcinogen activation, detoxification, and cellular repair may lead to individual differences in cancer risk and development.

The association of lung cancer with smoking exemplifies this type of genetic variation leading to cancer. We know that not everyone who smokes develops lung cancer. Researchers have begun to determine the reasons why this is so. Because most carcinogens require metabolic activation before binding to DNA, individuals with an elevated metabolic capacity to activate specific carcinogens may be at an elevated risk for cancer. A specific cytochrome p450 enzyme identified as CYP2D6 is known to metabolize debrisoquine, a drug commonly used to treat hypertension. People can be classified as poor, average, or extensive metabolizers of debrisoquine, which in turn is a functional assay for CYP2D6 activity and efficiency. We now know that extensive metabolizers are at increased risk of lung cancer (16). Thus, the genotyping of individuals facilitates assign-

ment of lung cancer risk on the basis of what level of metabolic activity exists in a given individual (17). Furthermore, understanding the genetic basis for differences in cancer risk due to carcinogen exposure offers deeper insight into how certain substances cause cancer. The demonstration that CYP2D6 protein can metabolize the tobacco-specific substance known as N-nitrosomnicotine (NNN) suggests a mechanism for associating extensive metabolizers of debrisoquine with elevated lung cancer risk (18).

A recent study (19) showed a relationship between cigarette smoking, N-Acetyltransferase-2 (NAT-2) polymorphisms, and breast cancer risk. These genetic changes result in decreased capacity to detoxify carcinogenic amines present in cigarette smoke. Although this observation is preliminary and deserves further study, one can imagine that multifactorial combinations of different enzyme activities could result in quite distinct cancer frequency and types in various individuals exposed to the same carcinogens.

11. What six factors may be responsible for individual susceptibility of patients to cancer?
 - a. _____
 - b. _____
 - c. _____
 - d. _____
 - e. _____
 - f. _____

12. What group of enzymes are involved in the conversion of a benign chemical substance into a highly reactive carcinogen capable of altering DNA?

THE IMPACT OF INDIVIDUAL GENOTYPES ON HIGH RISK FOR CANCER SUSCEPTIBILITY

Thus far, the discussion has centered on inherited differences in the abilities to handle a variety of exogenous environmental risk factors. Another set of individuals at risk for cancer are those who have inherited a mutation in an autosomal dominant cancer susceptibility gene. Suspicion of one of these hereditary syndromes is based largely on family history or disease characteristics, such as specific benign hamartomas of the face, tongue, soles, and palms in Cowden syndrome. Once this suspicion has been raised, presymptomatic testing may or may not be available to confirm the diagnosis on a molecular level. It is important to attempt a diagnosis of one of these syndromes when possible because it may significantly alter all phases of medical management of the individual and

his or her relatives. The issues of hereditary cancer susceptibility and genetic testing have been covered elsewhere (20). Persons with inherited cancer susceptibility syndromes such as breast and/or ovarian cancer due to BRCA1/2 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 for developing specific constellations of cancer types and are interested in knowing what they can do to lower their cancer risk.

The cancer risk-reduction options offered to persons carrying susceptibility mutations are generally classified as lifestyle change, chemoprevention, prophylactic surgery, risk reduction, and surveillance. Lifestyle suggestions often consist of altering diet, exercise, hormone replacement, and reproductive decisions. However, the effectiveness of these measures is still being evaluated in the general population, and there is even less known about whether these interventions work in persons known to carry a specific genetic mutation. There is insufficient research from controlled clinical trials to provide clear-cut guidance for prevention options in hereditary breast and colon cancers, and the best options currently available are risk-reduction recommendations based on anecdotal reports and expert opinion (21,22).

The use of prophylactic surgery is considered appropriate for some cancer syndromes but not others. Prophylactic surgery refers to the practice of removing healthy tissue at increased risk for development of a malignancy in the future. The rationale for surgery is that by removing an organ at risk for 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. It has even been suggested that choice of a specific surgical procedure (restorative proctocolectomy versus colectomy with ileorectal anastomosis) can be based on the exact location of the mutation found in the APC gene that causes FAP (23). Likewise, in MEN2, prophylactic removal of the thyroid may be effective because medullary thyroid carcinoma or its precursor lesion, C-cell hyperplasia are found in nearly 100% of studied individuals with MEN2 (24,25).

Unfortunately, there are several shortcomings to surgical prophylaxis. Problems such as the development of desmoid tumors in FAP patients after surgery can occur (26). In VHL, patients develop multiple renal cysts and tumors over time. If allowed to go untreated, these have a strong probability of becoming renal cell carcinomas, but ideal treatment of these renal lesions is controversial (27). If one performs total resection of the kidneys at initial

diagnosis of cysts or premalignant tumors, then the only remaining options are dialysis and transplantation. Alternatively, debulking of cysts and removal of individual tumors may prolong kidney function, but at the cost of repeated major surgeries. Although both approaches have extended survival of affected individuals, neither of these options is completely satisfactory.

In the case of hereditary breast cancer risk, prophylactic removal of one or both breasts often does not result in removal of all breast tissue. Therefore, a woman may reduce risk to an unknown degree but still have some residual risk for developing breast cancer. One recent retrospective study (28) estimated that the observed number of breast cancers among approximately 1,000 patients who underwent prophylactic mastectomy was significantly less than the expected number on the basis of age-adjusted population incidence rates alone. This study is very preliminary and would need to be replicated and extended before women at genetic risk are advised to get prophylactic mastectomies (22). In the meantime, prophylactic surgery is offered as an option to be carefully considered in the context of personal and cultural values and careful multidisciplinary consultations (29).

The situation is even more daunting for women at genetic risk for developing ovarian cancer. Medical surveillance for ovarian cancer is not as effective as that for colon or breast cancer, and survival rates for ovarian cancer are generally more dismal. Therefore, the woman at elevated risk for ovarian cancer has more motivation to consider prophylactic surgery. Unfortunately, there are published reports of malignancy occurring in the peritoneal lining that has the same embryonic origin as the ovaries after prophylactic oophorectomy (30). Experience currently suggests that surgical prophylaxis against ovarian cancer, while decreasing risk, fails to protect completely.

Another important limitation of risk-reduction measures in persons with inherited predisposition to cancer is that an increased risk is rarely confined to a single organ system. An example is HNPCC. Persons with an inherited HNPCC gene mutation are at risk for developing multiple colorectal cancers. Some people with the gene mutation may choose to have the colon removed when the first tumor is diagnosed to prevent additional tumors that are likely to occur. But these same individuals are also at risk for endometrial and ovarian cancer, as well as tumors of the upper gastrointestinal tract and urinary tract.

Information about surveillance for these risks are discussed in the next section. Issues currently under research and ethical investigation include determining criteria for when and what interventions are recommended for high-risk populations. It will be important in future research studies to determine which preventive risk-reduction tac-

tics might be best suited for specific populations or individuals. There is still a lot to learn about how to diagnose a genetic susceptibility to cancer, and then how to use the knowledge of cancer biology to effectively prevent or treat the disease (Figure 1).

13. What two sets of individuals are at increased risk for cancer?
 - a. _____
 - b. _____
14. What five cancer risk-reduction options does a person carrying susceptibility mutations have?
 - a. _____
 - b. _____
 - c. _____
 - d. _____
 - e. _____
15. What are limitations of prophylactic surgery?
 - a. _____
 - b. _____
 - c. _____

GENETICS IN CANCER SCREENING IN THE GENERAL POPULATION AND IN GENETIC HIGH-RISK POPULATIONS

Cancer screening or surveillance refers to the practice of identifying disease earlier than otherwise by systematically assessing individuals without symptoms. This differs from diagnosis, which generally involves thorough evaluation of an existing sign or symptom of disease. Criteria for determining cancer screening recommendations are currently based on age, family history, previous medical history of cancer, and other risk factors. Identifying individuals determined to be at increased cancer risk due

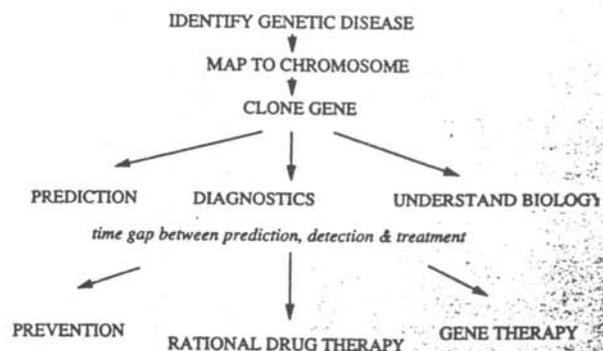


Fig. 1. Gene mapping timeline. (Adapted from Francis Collins, National Center for Human Genome Research, 1996.)

to inherited susceptibility is a new method of determining those who may benefit from screening practices. Ultimately, it may become possible to customize surveillance and diagnostic recommendations to this individual's profile of risk factors so that he or she can receive tailored screening (e.g., female BRCA1 and BRCA2 mutation carriers are screened at younger ages and more frequent intervals for both breast and ovarian cancer). Conversely, those who come from high-risk families with a known genetic mutation but who themselves test negative for that known familial mutation can then be spared the cost and anxiety of heightened 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 onset, such as VHL and MEN2, recommendations exist about what primary and secondary preventive courses of action to take and the efficacy of these strategies. However, the recommendations for breast, ovarian, and colon cancer are still evolving. Although the exact age to begin screening is still being hotly debated, women in the general population are advised to get regular mammograms sometime during their 40s (31,32,33). In contrast, those at higher genetic risk are often urged to begin mammography screening at younger ages (22).

For example, 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 (34). The National Institutes of Health and Department of Energy (NIH-DOE) Ethical Legal Social Implications (ELSI) Cancer Genetics Consortium has also issued recommendations regarding both BRCA1 and HNPCC screening (21,22). (Tables 2 & 3). Both sets of guidelines are based primarily on expert opinion and not

research data. These recommendations will continue to evolve and expand as more knowledge is gained through research.

Another issue that often arises is whether there are additional cancer risks introduced by the very methods used for cancer screening and diagnosis. There is currently some concern that certain subpopulations (e.g., those with radiation sensitivity) exist in which the benefits of mammography for detecting small, treatable cancers may not outweigh the risks. The amount of radiation exposure from a mammogram is minimal and generally not of significant carcinogenic danger to the average woman. However, for persons with an inherited radiation sensitivity (such as carriers of mutations in the Ataxia Telangiectasia gene), there may be an enhanced cancer risk from repeated mammography (35).

All of the preceding points make it clear that we need long-term follow-up of individuals known to carry specific mutations, so that the effects of various risk-reduction and screening strategies can be determined. Late in 1996, the Board of Scientific Advisors of the National Cancer Institute (NCI) approved funding for a proposed 5-year pilot Cancer Genetics Network that will seek to collect this data longitudinally. The request for proposals (RFP) for this network was published in May, 1997, inviting applications from organizations with demonstrated excellence in human cancer genetics for resource-related cooperative agreements, a new mechanism for the NCI (36). The purpose of this solicitation is to support the formation of a consortium that will serve as an infrastructure for collaborative research investigations into the genetic basis of human cancer susceptibility, explore mechanisms for integrating this information into medical practice, and identify means to address the psychosocial, ethical, and legal issues associated with human cancer genetics.

TABLE 2. Option for surveillance for carriers of BRCA1 and BRCA2 mutations*

Intervention	Provisional Recommendations
Breast self-exam	Education re: monthly exam
Clinical breast exam	Annually or semi-annually 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 semi-annually, beginning at age 25-35 y.
Prostate cancer surveillance for men who carry BRCA1 mutations only	Inform regarding options for screening involving DRE, PSA annually beginning at age 50 y.
Colon cancer surveillance	Follow ACS general population recommendations: e.g. FOBT annually and flex sig q. 3-5 y. beginning at age 50 y.

DRE, Digital Rectal Exam; PSA, Prostate Specific Antigen blood test; ACS, American Cancer Society; FOBT, Fecal Occult Blood Test; Flex sig q., Flexible Sigmoidoscopy.

*This table is based on U.S. Preventive Services Task Force criteria and level III evidence, i.e., expert opinion and case reports only. Recommendations in most cases are of unproven benefit, have limited screening sensitivity; there is also insufficient data to determine the screening interval or the optimal age to begin screening. (Adapted from Burke et al., 1997)

TABLE 3. Options for surveillance for carriers of HNPCC-Associated mutations*

Intervention	Provisional Recommendations
Colonoscopy	Begin at age 20-25 y., repeat every 1-2 y.
Transvaginal ultrasound or endometrial aspirate	Annually beginning at age 25-35 y.

*This table is based only on U.S. Preventive Services Task Force criteria, level II-3 (multiple-time series with and without the intervention), and level III (expert opinion). In most cases the benefits are not proven, screening sensitivity is limited, and there is often insufficient data to determine the screening interval or the optimal age to begin screening. (Adapted from Burke et al., 1997)

16. Define cancer screening or surveillance.

17. What four criteria are currently used to determine cancer screening of individuals?
 - a. _____
 - b. _____
 - c. _____
 - d. _____
18. Name two of the many groups that have issued recommendations for surveillance of individuals with inherited cancer susceptibility?
 - a. _____
 - b. _____

GENETICS IN CANCER DIAGNOSTICS

Precise cancer diagnosis is essential if we are to understand the pathophysiology of cancers, offer accurate prognosis, establish appropriate medical management, and develop more targeted methods of therapy. There may be several levels of diagnoses that could be made in an 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 due to symptoms or through positive results on a screening test, further diagnostic tests are undertaken. These may involve tests of blood, urine, or other bodily fluids; special imaging methods; or biopsy.

It is becoming increasingly common to incorporate genetic analysis into diagnostic workups, especially for the leukemias, in which chromosomal alterations seem fundamental to neoplastic transformation. These tests may be chromosomal analysis, flow cytometry, or molecular tests for specific genetic alterations. Specific recurring structural abnormalities of chromosomes are

being identified in increasing numbers of individuals. For example, the Philadelphia chromosome involving a translocation between chromosomes 9 and 22 is typical of chronic myelogenous leukemia (CML) (3). This chromosomal rearrangement leads to production of an abnormal protein fusion that contributes to poorly regulated control of cell growth that is characteristic of leukemia.

Another well-characterized molecular disturbance involves translocations seen in acute promyelocytic leukemia (APL). Several translocations involving chromosome 15 have been reported in APL. The 15;17 translocation in APL provides the critical connection between improvements in diagnosis leading to improvements in treatment. This translocation results in disruption of the retinoic acid receptor alpha (RARA) gene on chromosome 17 and of the promyelocytic leukemia (PML) gene on chromosome 15. The RARA is needed for stem-cell differentiation and maturation. Without it, there is cell arrest at the level of the promyelocyte, and this results in disruption of coagulation control, leading to the leukemic clinical manifestations. This knowledge provides the basis for a rational treatment approach to APL, which will be discussed in the later section on cancer treatment.

Another example showing the implications of using genetic information for diagnosis has to do with neuroblastoma. What appears to be a single disease may actually be a family of related diseases or subtypes of the disease. For example, neuroblastoma (NB) has been divided into several subtypes based on genetic findings in the tumor (i.e., diploid, hyperdiploid, triploid, and tetraploid karyotypes with or without deletion on 1p or amplification of the N-myc oncogene on chromosome 2p). This diagnosis of NB genetic subtype has implications for etiology, natural history, prognosis, and treatment of this cancer.

Another example of utilizing genetic information to make a diagnosis can be seen with pheochromocytoma. The clinical diagnosis of pheochromocytoma is established through biochemical testing, imaging, surgery, and histopathologic examination. However, the pheochromocytoma may have occurred sporadically or because the individual has an increased genetic susceptibility due to VHL, MEN2, or NF1. The recognition of an underlying genetic condition is important because this will affect the selection of medical management. Therefore, the oncology nurse needs to pay attention not only to clinical diagnosis, but also to genetic subtype and the potential for an underlying inherited cancer susceptibility syndrome, which can affect management of care (10).

19. Name three levels of diagnoses that could be made in an individual.
- _____
 - _____
 - _____
20. What cancer commonly has genetic analysis incorporated into diagnostic workups?
- _____

GENETICS IN CANCER PROGNOSIS

Genetic information may help the practitioner to identify factors that influence prognosis for disease outcomes. A prognostic factor is defined as any measurement available at the time of diagnosis or surgery that is associated with disease-free or overall survival. Traditional prognostic indicators 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 illustrate the impact that genetic analysis of cell proliferation, oncogenes, and tumor-suppressor gene alterations are having on the understanding of cancer prognosis.

There are a variety of techniques for measuring cell proliferation such as DNA flow cytometry and immunohistochemical staining (IHC) on either frozen or permanent tissue (37).

Replicative cell kinetics at the time of specimen collection can be estimated with flow cytometry, a technique that allows for the rapid quantitative measurement of cellular characteristics such as tumor size, surface marker expression, and DNA content. Flow cytometric cell cycle analysis is primarily directed at calculating the proportion of S-phase cells (i.e., those undergoing active DNA synthesis) and is used to identify rapidly dividing neoplasms. Normally, only a small proportion of cells in any given organ should be synthesizing DNA at any given moment. However, actively growing cancer cells have an increased amount of DNA synthesis to keep up with the accelerated cell division taking place. Therefore, an increase in the percentage of cells in the S-phase of the cell cycle as determined by a flow cytometry DNA histogram correlates with the rate of cell division in the tumor cell population and is a strong predictor of the long-term survival of the patient.

Molecular IHC or mutational 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 25%-30% of breast and ovarian tumors, and this oncogene amplification and/or overexpression is a reliable indicator of poor prognosis (38). Thus, the HER-

2/neu assays may be useful for differentiating patients a higher risk for cancer recurrence. This observation also has led to clinical research trials investigating the use of HER-2/neu monoclonal antibodies with chemotherapy to target specifically the cancer cells overexpressing HER-2/neu. This technique is discussed later in the section on cancer treatment.

Tumor-suppressor genes are also frequently mutated or deleted in cancer. These changes are generally somatic. The p53 gene is the most commonly mutated tumor-suppressor gene, with mutations found in at least half of all cancer types. Multiple studies have shown that p53 is an independent marker of prognosis in breast and other tumors (39). Abnormal p53 protein is associated with decreased survival. The predictive usefulness of p53 status in breast tumors is further enhanced if p53 status is combined with other prognostic indicators such as family history and lymph node status (40).

Research continues to assess other genetic factors that can serve as prognostic factors. These experimental markers on the horizon of clinical care include metastasis suppressor factors such as nm23, measures of invasiveness such as cathepsin D, plasminogen activators and inhibitors, cell adhesion molecules, factors associated with angiogenesis, and telomerase. It is predicted that panels of molecular prognostic factors will be developed and widely utilized in clinical practice. As molecular markers based on the individual patient's tumor biology replace more generic prognostic indicators such as age, the accuracy of predicting patient outcome is expected to increase.

21. In what three areas may genetic analysis assist current cancer prognosis research?
- _____
 - _____
 - _____
22. Name three oncogenes, tumor-suppressor genes, or other molecular prognostic factors for cancer currently being studied.
- _____
 - _____
 - _____

GENETICS IN MONITORING FOR MINIMAL RESIDUAL DISEASE

Recurrences of cancer are often caused by small amounts of cancerous tissue remaining in the body after surgery or treatment. Such cancer is therefore called residual disease.

Monitoring for minimal residual disease is an important aspect of cancer care. The malignant cells may be in

the margins of a malignancy, which could present as a local recurrence, or in circulating cells, which could lead to distant metastases. The value of molecular genetics techniques is their use for detecting residual disease in situations that appear normal by other criteria such as histopathology. In one study, p53 analysis was used to evaluate patients with primary squamous cell carcinoma of the head and neck (41). Although all the patients appeared to experience a complete tumor resection on the basis of negative surgical margins, about half had positive margins by molecular analysis for p53 mutations. On follow-up, 38% of those with p53 mutations identified in cells from the apparently normal tissue surrounding the malignancy had locally recurrent carcinomas, whereas none of the patients with negative p53 molecular analysis in surrounding tissue had recurrences. Furthermore, molecular p53 analysis identified neoplastic cells in about 20% of lymph nodes that had been called negative by traditional assessment. Thus molecular analysis of surgical margins and lymph nodes has the potential to augment standard histopathologic assessment and may improve the sensitivity of detection for residual disease.

Application of molecular technologies to detect distant metastases is beginning to transfer from research to clinical practice. The principle is that metastatic cells often cannot be detected until they cause tissue damage sufficient for detection on clinical examination or current imaging techniques such as bone scans. Use of PCR combined with molecular markers of neoplasia has the potential to detect very small numbers of metastatic cells before they have had a chance to do further damage. This is dependent on the dual abilities of this technique to determine a characteristic of the metastatic cells that sets them apart from normal cells and to develop a method to reliably detect that difference. For example, molecular evaluation of a cytokeratin known as K19 in the bone marrow of breast cancer patients undergoing high-dose chemotherapy is useful in detecting occult metastases (42). Studies have shown that K19 positivity in the bone marrow of these patients is associated both with advanced stage of disease and poor prognosis. Detection of these metastases could alter treatment options and, hopefully, the clinical outcome.

23. Why would using molecular genetics techniques to detect minimal residual disease be of value?

24. Name two specific genetic tests used to detect residual disease.

- a. _____
- b. _____

GENETICS IN CANCER TREATMENT

The classical methods of treating malignancies are surgery, radiation, and chemotherapy. The choice of a particular treatment depends chiefly on the type and stage of the cancer. Genetic factors are expected to increasingly influence treatment decisions.

Most chemotherapeutic agents act either by damaging DNA directly or by interfering with DNA synthesis or repair so that the cancer cells cannot continue proliferating. The antimetabolites either inhibit cellular enzymes responsible for synthesis of DNA precursors or DNA itself. Alkylating agents react directly with DNA molecules to induce different types of DNA damage, including breakage and formation of abnormal cross-links between opposite strands of DNA. Other drugs target enzymes essential for the breakage and rejoining of DNA strands during replication. There are a variety of other drugs targeting various DNA and RNA structures and functions or the cell cycle.

There are several drawbacks to standard chemotherapies. One is that some cancer cells are resistant to a particular drug, and others develop resistance to multiple different drugs simultaneously. Another drawback of standard chemotherapy is that these drugs affect not only cancer cells, but also any normally dividing cells in the body, thus leading to the common toxic side effects. Approaches currently being utilized to overcome these deficits include combination chemotherapies, bone marrow transplantation to accommodate very high-dose chemotherapy treatments, and immunotherapy to help the body's natural defenses.

Rational drug therapies are individually tailored on the basis of the malignancy's molecular characteristics. This approach exploits features of the malignant phenotype which include rapid and unlimited growth, invasiveness, metastatic potential, and the ability to produce angiogenesis. Successful application of rational drug therapy is shown in the treatment of APL with all-transretinoic acid (ATRA). This treatment is based on knowing the basic genetic defect of a chromosomal translocation disturbing the RARA. Disruption of the RARA gene or blocking its response element by any one of several possible translocations leads to reduced functional amount of its product, RARA. Standard treatment now consists of replacing RARA with the medication, ATRA, which appears to reverse the arrest in maturation of malignant promyelocytes due to 15;17 chromosomal translocation, allowing them to undergo normal maturation and death. ATRA has been effective in treating most patients with relapsed or refractory APL and in inducing remission in previously untreated patients. Multiple outcome studies of treating APL with ATRA indicate a high response rate and less morbidity and equivalent mortality in

comparison with conventional chemotherapy. It is of interest that this treatment works for most chromosomal translocations associated with APL, but not for the 11;15 translocation. Thus, cytogenetic studies not only lead to rational drug therapy, but also to increasingly accurate predictions of biologic response based on the underlying genetic basis for the malignancy.

Another approach is to increase the specificity in targeting cancer cells with biologic therapies. Novel strategies 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 (43). Studies are underway in patients with extensively pretreated metastatic breast cancer that overexpress HER-2/neu using recombinant humanized monoclonal antibody to HER-2/neu (44).

Although most of these and other similar treatments are in basic research or early clinical trials, the trend toward increasing specificity of treatment modalities can be expected to continue finding its way into clinical practice.

Before leaving the topic of treatment, one final consideration deserves notice: that of treatment decisions for persons with inherited susceptibility to cancer. Persons carrying mutations in cancer susceptibility genes have unusually high risks for development of multiple neoplasias. For breast cancer patients, mastectomy versus lumpectomy plus radiation may not represent equally viable options if a particular patient has a 60% chance of developing a second tumor, as do some carriers of BRCA1 mutations, or if a patient has a genetic sensitivity to carcinogenic effects of radiation, as do ATM mutation carriers (see previous section on Genetics in Cancer Screening in the General Population). Therefore, treatment of an initial tumor in such a person may differ from that recommended for an individual without the genetic predisposition. In colon cancer treatment for example, bowel-conserving surgery at diagnosis of a carcinoma or dysplastic adenomatous polyp may not be in the person's best interest if the likelihood of subsequent colon malignancies is high. In summary, treatment decisions could be altered due to underlying genetic susceptibility.

25. What are two treatments based on molecular characteristics of a particular cancer?
- _____
 - _____

GENE THERAPY

Future options for cancer treatment will undoubtedly include gene therapy. The goal of gene therapy is to cor-

rect a gene alteration in a cell in order to prevent, treat, or cure disease caused by a malfunctioning gene. Gene transfer requires that a functional gene be transferred to the appropriate tissue to achieve correction of the gene error or mutation.

Most clinical cancer genetic research trials are currently focused on investigating diagnostics, or on repair or replacement of defective genes.

Categories of gene therapy include (a) germline gene transfer, in which the gene corrections are made to the reproductive egg or sperm cells to correct future inherited illnesses, and (b) somatic cell gene therapy, in which nonreproductive organs are targeted. Germline gene transfer has grave ethical implications regarding possibilities of eugenic misuses to remove undesirable traits from the population or to effect human enhancement by providing genes that enhance specific desirable traits. To prevent inappropriate applications or eugenic misuses, the ethical implications of genetic technologies applications must always be carefully considered.

Only somatic gene therapy for the transfer of corrected or altered genes to body cells has been approved for clinical trials. 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 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. Examples of biologic vectors are retroviruses, adenoviruses, and plasmids. Nonviral methods of gene transfer such as chemical transfer and liposomes, as well as direct microinjection of DNA, RNA, or their protein products are under investigation.

Current gene therapy studies for cancer have been reviewed in recent articles (45,46). These studies include marker gene protocols that utilize gene-marked cells to track outcomes of introduced gene therapy cells or other cells of interest. Other protocols are assessing the effectiveness and safety of genes that target genetic alterations thought to cause cancer, such as the p53 gene. A number of studies are transferring genes to add a new function to cells such as inserting the MDR (multidrug resistant) gene to modify response of cells to toxic chemotherapy (47). There are still critical drawbacks in these strategies preventing widespread application. Especially vexing are barriers to the development of successful vectors for delivering the gene therapies to target cells other than bone marrow. Preliminary studies are beginning to shed light on the effectiveness and toxicities of gene therapy.

26. What is the goal of gene therapy?
- _____

27. What type of gene transfer has been approved for clinical trials?

28. What type of gene transfer has NOT been approved for clinical trials?

29. What are two approaches for delivery of corrected or altered genes to body cells?
a. _____
b. _____
30. What five areas are important for the oncology nurse to incorporate into practice regarding genetic applications to cancer care?
a. _____
b. _____
c. _____
d. _____
e. _____

CONCLUSION: THE NURSE'S ROLE

The introduction of genetic technologies into oncology practice is exciting because of the potential future implications for reducing morbidity and mortality. However, every new innovation has consequences, medical as well as personal, social, ethical, and legal. The nurse working with oncology patients and their families has an important role in ensuring the safety of patients involved in genetic studies. As direct caregiver, the nurse has opportunities to monitor the patient for responsiveness and outcomes of diagnosis and treatment. Providing education to the patient and family about how gene tests are done, how gene therapy is administered, potential side effects, and other questions of concern is a crucial responsibility. Nursing research has the potential to address many areas of concern in this practice setting. Helping to design safe applications of genetic technologies for cancer risk reduction, surveillance, diagnosis, and treatment will enhance options for future patient care.

Nurses must begin to think of genetic technology as applicable to all cancer patients. 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 for cancer. Learning how to screen and manage high-risk patients as a result of better genetic technologies offers challenges to health care resources. Information about referral to clinical trials can be made by calling the NCI Cancer Information Service at 1-800-4-CANCER. The American Cancer Society information line at 1-800-ACS-2345 has a great amount of patient and professional information available. At their regional offices throughout the country, information specialists stand ready to help the practicing nurse answer patient questions pertaining to the latest developments in cancer care.

The next programmed instruction module will consider the role of the nurse in cancer genetics and provide additional information to consider for practice in cancer care.

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Programmed Instruction: Answers

PRETEST

- | | |
|----------|-----------|
| 1. True | 9. True |
| 2. True | 10. True |
| 3. True | 11. True |
| 4. False | 12. True |
| 5. False | 13. False |
| 6. False | 14. True |
| 7. True | 15. True |
| 8. True | |

CONTENT QUESTIONS

1. a. Understanding of cancer causes
b. Risk reduction or prevention
c. Diagnosis
d. Treatment
e. Prognosis information
2. a. Polymerase chain reaction (PCR) methods
b. Methods combining molecular and cytogenetic techniques
c. Miniaturization, automation, computerization
3. Full gene sequencing
4. The cancer genome anatomy project will provide information about which genes are expressed in normal, precancerous, and malignant tissues.
5. a. Avoid factors known to be carcinogenic.
b. Thwart the biologic onset of cancer through altered lifestyle, chemoprevention, or prophylactic surgery.
6. Long, multistep, multimutation process proceeding from hyperproliferation of colonic epithelium to polyp formation, adenoma growth and increasing dysplasia, and possible invasive malignancy
7. 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
8. a. Retinoids: oral leukoplakia, squamous cell carcinoma of the head and neck
b. Tamoxifen: breast cancer
c. Finasteride: prostate cancer
d. Aspirin: colorectal adenoma
9. a. Enrollment of healthy individuals rather than cancer patients
b. Confidentiality in recruitment
c. Enrollment of high-risk subjects
d. Randomization to placebo arms that may offer no benefit to the individual
e. Obtaining adequate informed consent
f. Clinical trial monitoring
g. Possible conflicts of interest between researchers and participants
h. Competing outcomes and toxicities
10. Molecular genetics is now giving researchers the tools to make possible the assessment of intermediate biomarkers that are indicative of progression along the carcinogen pathway. These biomarkers will make it possible to select study populations on the basis of tumor characteristics and genetic susceptibility.
11. a. Differences in metabolism of carcinogenic uptake, activation, and detoxification
b. DNA repair variations
c. Inherited or acquired mutation in specific proto-oncogenes or tumor-suppressor genes
d. Nutritional status
e. Hormonal factors
f. Immune system factors
12. Cytochrome p450 enzymes
13. a. Individuals who lack ability to handle a variety of exogenous environmental risk factors
b. Individuals who have inherited a mutation in an autosomal dominant cancer susceptibility gene
14. a. Lifestyle change
b. Chemoprevention
c. Prophylactic surgery
d. Risk reduction
e. Surveillance
15. a. May develop other complications such as the development of desmoid tumors in FAP patients or the need for dialysis and transplantation in patients with VHL
b. May not remove all the tissue
c. Cancer occurs in multiple organs; not all organs can be removed.

16. The practice of identifying disease earlier than otherwise by systematically assessing individuals without symptoms
17.
 - a. Age
 - b. Family history
 - c. Previous medical history of cancer
 - d. Other risk factors
18.
 - a. International Collaborative Group for the Study of HNPCC (ICG-HNPCC)
 - b. The NIH-DOE Ethical, Legal, Social Implications Cancer Genetics Consortium for Breast cancer and HNPCC
19.
 - a. Clinical diagnosis of a specific malignancy
 - b. The genetic subtype of that malignancy
 - c. The genetic diagnosis of an underlying cause for that malignancy
20. Leukemia
21.
 - a. Characterizing cell growth and proliferation
 - b. Detecting oncogene mutations or amplifications
 - c. Detecting tumor-suppressor gene mutations, inherited and somatic
22.
 - a. HER-2/neu
 - b. p53
 - c. nm23, cathepsin D, plasminogen activators and inhibitors, cell adhesion molecules, angiogenesis factors, or telomerase
23. Potential to augment standard histopathologic assessment and possibly improve sensitivity of detection of residual disease
24.
 - a. Squamous cell carcinoma of the head and neck: p53 analysis
 - b. Breast cancer: molecular evaluation of cytokeratin K19 in the bone marrow
25.
 - a. Rational drug therapy that exploits features of the malignant phenotype such as the use of ATRA for relapsed or refractory APL
 - b. Biologic therapies to target specific cancers such as the use of recombinant humanized monoclonal antibody to HER-2/neu
26. Correct a gene alteration of a cell to prevent, treat, or cure disease caused by a malfunctioning gene
27. Somatic gene therapy for the transfer of corrected or altered genes
28. Germline gene transfer
29.
 - a. Ex vivo route, which takes the cells of interest from the patient, corrects the genetic defect in these cells while in an external lab setting, and then returns them to the patient
 - b. Direct gene transfer in vivo, which involves introducing corrected gene directly into the cells of the body
30.
 - a. Ensuring the safety of patients involved in genetic studies
 - b. Monitoring the patient for responsiveness and outcomes of diagnosis and treatment
 - c. Providing education to the patient and family about how gene tests are done, how gene therapy is administered, and potential side effects
 - d. Conducting research for this practice setting
 - e. Participating in the design of safe applications of genetic technologies for cancer risk reduction, surveillance, diagnosis, and treatment

Programmed Instruction: Posttest

CLINICAL APPLICATIONS OF GENETIC TECHNOLOGIES TO CANCER CARE

Match the following statements with the correct word:

1. The avoidance of factors known to be carcinogenic.
2. 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.
3. The practice of identifying disease earlier than otherwise by systematically assessing individuals without symptoms.
4. Takes cells of interest from the patient, corrects the genetic defect in these cells while in an external lab, and then returns them to the patient.
5. The corrected gene is introduced into the cells of the body.
 - a. Cancer risk reduction
 - b. Surveillance
 - c. Chemoprevention
 - d. Direct gene transfer
 - e. Ex vivo gene therapy

Choose the best response for each statement:

6. Understanding cancer at the cellular level will improve cancer management by all of the following except by
 - a. Selecting well-defined populations for risk reduction, early diagnosis, and treatment
 - b. Providing information to insurance companies
 - c. Increasing accuracy and specificity of diagnosis, treatment, and prognosis
 - d. Modifying standard risk reduction and treatment options.
7. Genetic technology will move cancer care forward by
 - a. Determining who will get treatment
 - b. Determining who gets insurance coverage
 - c. Determining more precise molecular diagnosis to complement clinical findings
 - d. None of the above.
8. Risk reduction can be accomplished by which of the following
 - a. Lifestyle change
 - b. Chemoprevention
 - c. Surgery
 - d. All of the above.
9. The agent being studied as a chemopreventive agent for colon cancer is
 - a. Tamoxifen
 - b. Aspirin
 - c. Retinoid
 - d. Finasteride.
10. Individual susceptibility to cancer occurs by
 - a. Differences in metabolism of the carcinogen
 - b. DNA repair variations
 - c. Nutritional status
 - d. Hormone influences
 - e. All of the above
 - f. a and b only.
11. A smoking person's susceptibility to lung cancer is an example of
 - a. Genetic variation resulting from metabolism of carcinogens
 - b. Chemoprevention
 - c. Lifestyle
 - d. None of the above.
12. Prophylactic surgery is used for which cancer(s)?
 - a. Colon cancer
 - b. Breast cancer
 - c. Sarcoma
 - d. a and b only
 - e. None of the above
13. Genetic intervention in diagnosis is currently used for
 - a. Chronic myelogenous leukemia
 - b. Acute promyelogenous leukemia
 - c. None of the above
 - d. a and b.
14. The cancer prognosis technique(s) used for measuring cell proliferation is/are
 - a. Flow cytometry
 - b. Immunohistochemical staining
 - c. None of the above
 - d. All of the above.
15. Which oncogene is amplified in breast and ovarian cancer and is used as a reliable indicator of poor prognosis?
 - a. bcl-1
 - b. bcl-2
 - c. HER-2/neu
 - d. p53

16. The combination of which protein with family history and lymph node status provides predictive usefulness in breast cancer?
 - a. p53
 - b. HER-2/neu
 - c. bcl-1
 - d. bcl-2
17. The ability to treat cancer through rational drug therapy is based on
 - a. The malignant phenotype
 - b. Molecular characteristics of the malignancy
 - c. a and b
 - d. None of the above.
18. Clinical cancer genetic research is currently focusing on
 - a. Diagnostics
 - b. Treatment
 - c. Repair
 - d. Replacement
 - e. All the above.
19. The standard for detecting genetic mutations is
 - a. Full gene sequencing
 - b. Complete blood count
 - c. Urinalysis
 - d. None of the above.
20. Oncology nurses are incorporating genetics into their practice by
 - a. Ensuring safety of patients on genetic studies
 - b. Monitoring patient outcomes to diagnosis and treatment
 - c. Providing education
 - d. Participating in the design of safe applications of genetic technologies
 - e. All of the above
 - f. a, b, and c only.

Continuing Education Credit: Clinical Applications of Genetic Technologies to Cancer Care

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INSERT YOUR ANSWERS FOR GENETIC TESTING FOR CANCER PREDISPOSITION

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- | | |
|-----------|-----------|
| 1. _____ | 11. _____ |
| 2. _____ | 12. _____ |
| 3. _____ | 13. _____ |
| 4. _____ | 14. _____ |
| 5. _____ | 15. _____ |
| 6. _____ | 16. _____ |
| 7. _____ | 17. _____ |
| 8. _____ | 18. _____ |
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- | | | | | | |
|--|---|---|---|---|---|
| I. How well were you able to meet the Programmed Instruction stated objectives? | | | | | |
| • Describe the impact of understanding molecular carcinogenesis on cancer management. | 1 | 2 | 3 | 4 | 5 |
| • Discuss the genetic basis for differences in cancer risk resulting from carcinogen exposure. | 1 | 2 | 3 | 4 | 5 |
| • Describe risk reduction and screening recommendations for persons with inherited breast, ovarian, and colon cancer susceptibility syndromes. | 1 | 2 | 3 | 4 | 5 |
| • Describe the current and potential utilization of genetic knowledge in cancer diagnosis, prognosis, and treatment. | 1 | 2 | 3 | 4 | 5 |
| II. Was the content relevant to the objectives? | 1 | 2 | 3 | 4 | 5 |
| III. Did this method of presentation facilitate your learning? | 1 | 2 | 3 | 4 | 5 |
| IV. Was the content appropriate to your area of practice? | 1 | 2 | 3 | 4 | 5 |
| V. Did the content contribute to meeting your personal learning objectives? | 1 | 2 | 3 | 4 | 5 |

Length of time taken to review the study guide (circle one)
1 h 1.5 h 2 h 2.5 h 3 h