OVERVIEW

I. Organization and function of genetic material
   A. Chromosomes are threadlike structures that contain genetic information.
      1. The 46 chromosomes in the human body are made up of 23 chromosome pairs, one copy from each parent.
         a. The small arm of the chromosome is identified as the “petite” or “p” arm of the chromosome.
         b. The large arm is labeled the “q” arm, because “q” follows “p” (Figure 5-1).
      2. Autosomes represent the 22 chromosome pairs, numbered 1 to 22, which do not determine sex.
      3. Sex chromosomes are the X and Y chromosomes, which determine an individual’s sex.
         a. Women have two X chromosomes.
         b. Men have one X chromosome and one Y chromosome.
   B. Nucleic acids consist of bases and a sugar and phosphate group. Two types of nucleic acids exist.
      1. Deoxyribonucleic acid (DNA) comprises two nucleotide chains, running in opposite directions and held together by hydrogen bonds, which are coiled around one another to form a double helix (Figure 5-2).
         a. In DNA, two types of bases are present: purines and pyrimidines.
            (1) Two types of purines: adenine (A) and guanine (G)
            (2) Two types of pyrimidines: thymine (T) and cytosine (C)
         b. DNA base pairs are complementary on the double strand; A attaches to T, and G attaches to C.
      2. Ribonucleic acid (RNA) consists of a single nucleotide chain, which represents a complimentary copy of a strand of DNA.
         a. In RNA, the bases are the same as DNA except the base uracil (U) replaces thymine (T).
         b. Transcription refers to the process of making RNA from DNA.
         c. Translation refers to the process of making proteins from RNA.
         d. Proteins consist of chains of amino acids. Sequences of the amino acids determine the function of the protein.
         e. Primary types of RNA (Figure 5-3)
            (1) Messenger RNA (mRNA) contains information about the order of the amino acids in a protein.
               a. A codon is a chain of three mRNA nucleotides that specifies the production of one of 20 different amino acids.
               b. More than one codon will code for a specific amino acid.
               c. An mRNA nucleotide change in the third place of the codon rarely causes an amino acid change. A change in the first place of the codon usually will cause a different amino acid to be produced and an error in building the protein. These changes are the direct cause of polymorphisms and mutations.
               d. Three “stop” codons and the associated RNAs stop the growth of the amino acid chain.
                  (i) Transfer RNA (tRNA) brings the amino acids to the site of protein synthesis.
                  (ii) Ribosomal RNA (rRNA) provides the structural support for the protein in addition to other functions.
                  (iii) Small silencing RNAs have important roles in gene regulation. These include microRNA (miRNA), Piwi-interacting RNA (piRNA) and small interfering RNA (siRNA) (Ghildiyal & Zamore, 2009).
C. As seen in Figure 5-1, genes are individual units of hereditary information, which are located at a specific position on the chromosome.
1. Genes consist of a sequence of DNA that codes for a specific protein (see Figure 5-1).
2. Genes consist primarily of exons and introns.
   a. Exons are protein-coding segments of a gene.
   b. Introns are non-protein-coding segments or the sequence-interrupting piece of a gene.

II. Basic mechanisms of carcinogenesis, mutations, and heredity
A. Cancer has a multifactorial etiology with several genetic, environmental, and personal factors interacting to produce a malignancy.

B. Genetic mutations and genetic instability are at the very core of cancer development. Most cancers are not the result of inherited mutations.
1. Most cancers are associated with genetic mutations that occur in single cells some time during the life of an individual.
2. A malignant tumor arises after a series of genetic mutations have accumulated.
B. Genetic mutations that are acquired are associated with exogenous (environmental) or indigenous factors (biologic). For example, carcinogens are exogenous factors thought to operate by causing genetic mutations.
C. Mutations are disease-causing variations in the sequence of DNA.
1. Genetic mutations are usually acquired over a lifetime. These are designated as somatic and are acquired genetic mutations in body cells that occur after conception.
2. In a person with a genetic predisposition to cancer, a mutation has been inherited in the germline reproductive cells.
3. Types of mutations
   a. Frameshift mutations occur when one or more bases are added or deleted from the normal sequence, resulting in an altered form of the protein.
   b. Missense mutations are single-base pair changes that result in the substitution of one amino acid for another in the protein being constructed. Some of the substituted amino acids may be critical to the function of the protein.
   c. Nonsense mutations change an amino acid signal into a signal to stop adding amino acids to a growing protein. Nonsense mutations result in a truncated, presumably nonfunctional, protein.
   d. RNA-negative mutations result in the absence of RNA transcribed from a gene copy.
e. Splicing mutations occur when DNA that should be removed from the coding sequence is retained or when DNA that should not be added is spliced in, resulting in frameshift mutations.

f. Polymorphisms are changes in the DNA sequence of a gene that often are not disease related, occur at variable frequency, and are associated with individualization in the general population. A single nucleotide polymorphism (SNP, pronounced “snip”) is a DNA change in one nucleotide.

4. Chromosomal abnormalities
   a. Translocations refer to segments of one chromosome that break off and attach themselves to other chromosomes, resulting in altered protein production.
   b. Aneuploidy is an abnormal number of chromosomes.
   c. Loss of heterozygosity refers to the loss of a segment of both copies of a chromosome.
   d. Microsatellite instability (MSI) segments are repetitive pieces of DNA scattered throughout the genome in the noncoding
regions (introns). MSI is a marker of germline abnormality in mismatch repair genes in colorectal cancer, also known as Lynch syndrome. If MSI is identified in sporadic cases, it is referred to as gene hypermethylation.

D. A malignant tumor is derived from genetic instability and genetic mutations in genes that control cell growth and proliferation.

1. Types of regulatory genes
   a. Proto-oncogenes are normal genes essential for normal cell growth and regulation. Mutations occurring in proto-oncogenes convert to oncogene activation, which may result in uncontrolled cell division.
   b. Tumor suppressor genes function as regulators of cell growth. Some tumor suppressor genes appear to play a role in cell cycle regulation, whereas others have a role in DNA repair. Cells with mutation of a tumor suppressor gene may develop uncontrolled cell growth.
   c. DNA repair genes
      (1) Mismatch repair (MMR) genes are a type of DNA repair genes responsible for keeping the DNA free of “changes” during DNA synthesis. MMR genes are associated with microsatellite instability in Lynch syndrome.
      (2) Mutations in DNA repair genes may be inherited from a parent or acquired over time because of aging or carcinogens from the environment.

2. Mutator phenotype
   a. The mutator gene phenotype allows an increased mutation of genes because of poor proofreading or insertion of incorrect nucleotides left unrepixed. They seem to be efficient at acquiring mutations with both clonal and random mutations, allowing thousands of mutations versus lower rates seen with normal cells (Loeb, 2011).
   b. DNA damage that is overlooked by repair mechanisms may lead to incorrect messages in the DNA sequences, offering increased chance of oncogene mutations. If this occurs, “driver” mutations offer a growth advantage.
   c. “Passenger” mutations are those nucleotide changes that do not provide a growth advantage.

3. Control of cell growth and proliferation
   a. Apoptosis refers to the activation of a program that leads to normal, programmed cell death and often occurs in response to DNA damage. Malfunction results in uncontrolled cell proliferation of damaged and malignant cells.
   b. Telomerase plays a role in cellular aging through the telomeres, which are the ends of the chromosome.
      (1) As cells age, telomerase is normally repressed, and the telomeres are progressively lost.
      (2) In cancer, telomerase is reactivated, which keeps the telomeres intact, facilitating cell immortalization.

4. Cancer theories
   a. Knudson’s two-hit damage hypothesis refers to the inactivation of both copies of a given regulatory gene. Because all individuals are born with two copies of almost every gene, Knudson originally theorized that both functioning copies of the gene must be inactivated for cancer to occur. Now, on the basis of molecular-level research, it is known that one hit may exist, as seen with chronic myeloid leukemia (CML), that two hits cause retinoblastoma, and that many hits over time cause cancers, such as colorectal cancer (Knudson, 2001).
   b. Viral (retrovirus) infections copy a piece of RNA genome into the human DNA by using viral reverse transcriptase. Once the viral DNA or RNA (viral oncogene) is integrated into the human genome, it is transcribed by host RNA polymerase, causing mRNA to be translated into a nonfunctioning protein and resulting in cell proliferation (Rickinson & Kieff, 2001).
   c. The inflammation theory of cancer development notes that a variety of infectious agents and their relationships with inflammatory cells are the primary causes of cancer, proliferation, survival, and migration of cancer cells. From the innate immune system, selectins, chemokines (e.g., nuclear factor κB [NFκB]) and their receptors encourage invasion, migration, and metastasis (Coussens & Werb, 2002; Kawanishi, Hiraku, Pinlaor, & Ma, 2006).

E. Mendelian inheritance
   1. Autosomal dominant inheritance requires only one altered copy of a gene to result in disease expression (Figure 5-4).
   2. Autosomal recessive inheritance requires two altered copies of a gene, one from each parent, to result in disease expression (Figure 5-5).
   3. X-linked inheritance is associated with the inheritance of genes located on the X chromosome. Men carry one X and one Y chromosome, and genes on their X chromosome are hemizygous (having only one copy of a chromosome pair), so a mutation in a gene on an
X chromosome in a man may result in disease expression.

III. Key technical characteristics of predisposition genetic testing and tumor profiling

A. Techniques for identifying mutations

1. Direct sequencing
   a. Determines the sequence of the gene being tested and detects sequence changes in the regions being analyzed
   b. Detects sequence changes in the regions being analyzed but may miss mutations outside the coding region or mutations that are large genomic rearrangements or large deletions

2. Allele-specific oligonucleotide (ASO)
   a. Detects one single specific mutation that involves a short sequence of DNA

3. Genome-wide association studies (GWAS)
   a. Survey the entire genome for small nucleotide alterations and do the following:
      (1) Detect SNPs or small mutations to determine association with disease (NCI Dictionary of Genetic Terms, n.d.)
      (2) Review for changes with specific disease (cancer type) versus people without the disease
      (3) Design high-throughput genome sequencing techniques to offer faster and cheaper ways to obtain genetic data, with potential impact on personalized profiling for diagnosis, pharmacogenomics, and disease monitoring (Soon, Hariharan & Snyder, 2013)

4. Single-strand confirmation polymorphism analysis (SSCP)
   a. A sequence change of DNA alters the size and shape of a DNA fragment, which is detected by SSCP on a gel.
   b. An altered gene produces a gel band different from that produced by a normal gene.
   c. SSCP easily detects insertions or deletions of four or more bases of DNA; however, mutations exchanging one base for another without altering the length of the DNA fragment are difficult to detect. In this technique, gel electrophoresis separates different conformations of the strands prior to sequencing.

5. Large genomic rearrangements (LGRs)
   a. Detect large rearrangements, deletions, and duplications (like pages or paragraphs missing or rearranged in a mystery novel)
   b. Found in BRCA1 family mutations:
      (1) At least two persons younger than 50 years diagnosed with breast cancer
      (2) Family history of breast and ovarian cancers
      (3) Only ovarian cancer, with at least two members diagnosed with ovarian cancer
      (4) A single breast cancer case prior to the age of 36 years
      (5) None identified in only one breast cancer case prior to age 51 (Engert et al., 2008)

6. Microarray
   a. Technique attaches large numbers (hundreds to thousands) of DNA, RNA, protein, or tissue segments to slides specific locations on the slide, followed by application of a fluorescent label. The biosample is processed so that the genetic material of the sample
binds to the genetic material on the slide. The slide is scanned to measure the brightness of each fluorescent dot. The brighter the dot, the greater is the fluorescent activity (Figure 5-6).

b. Microarray is used for mutation detection as well as gene expression.

7. Next-generation DNA sequencing (second-generation sequencing)
a. New, lower-cost, higher-efficiency techniques to target the whole genome, whole exome, and whole transcriptome
b. Detect somatic cancer genome alterations of the nucleotide (substitutions, small insertions, deletions, variations in copy number)

8. Whole-exome sequencing (WES) or targeted exome capture
a. Low-cost alternative technique to sequence exon (gene to protein-coding regions) pieces of the genome
b. Identifies area of protein function change in mendelian and common diseases

9. Transcriptome sequencing
a. Analyzes coding RNA molecules and non-coding RNA sequences in one or specific populations of cells (Meyerson, Gabriel, & Getz, 2010)

10. Sequential analysis of gene expression (SAGE)
a. Provides a picture of the mRNA population in a cancer sample

11. Protein truncation assay
a. Refers to an analysis of coding DNA, directly translated in the laboratory into protein
b. Shortened proteins detected on a gel, based on mobility differences between larger and smaller proteins
c. Sensitive for detection of mutations in which the sequence change results in a shortened form of the protein but does not detect other types of mutations

B. Techniques to identify chemical modification or packaging of DNA
1. Review methylation across entire genome (methylome)
a. Addition of methyl groups to GC-rich region of DNA
b. Hypomethylation with removal of methyl groups causing inactivation of a gene
2. Methylation pattern of genes by tissue type

C. Considerations in genetic testing laboratory selection
1. Laboratories where genetic testing is performed should meet the following criteria:
   a. Clinical Laboratory Improvement Act (CLIA)–approved laboratory
   b. Does not evaluate proficiency of DNA testing
   c. Laboratory director certified by the American Board of Medical Genetics

2. Research in which genetic research is performed in institutional laboratories with oversight to ensure meeting biosafety standards such as the NIH Guidelines for Research Involving Recombinant DNA Molecules (http://oba.od.nih.gov/oba/rac/Guidelines/NIH_Guidelines.htm)

IV. Use of genetic markers for diagnosis

A. Cytogenetics focuses on the structure, function, and abnormalities of chromosomes (Jorde, 2009). It is commonly used to diagnose both solid and hematologic malignancies.

1. Karyotype offers a view of the number and structural appearance of chromosomal structures in the cell nucleus (Lobo, 2008) (Figure 5-7).
   a. Balanced structural change in chromosomes with evenly exchanged genetic material; for example, Philadelphia chromosome translocation of 9;22, which yields an abnormal chromosome but genetic material amount remains constant although reshuffled (Figure 5-8)
   (1) Chromosomal rearrangement example: CML with the hybrid bcr-abl gene
   (2) Some thyroid cancers associated with rearrangements in the RET gene
b. Nonreciprocal change of chromosomes with unequal genetic material to be lost or gained
   (1) Deletions or inactivation of a gene on a chromosome begin the process of accumulation of genetic variation, which then initiates cancer development. Tumor suppressor genes are an example of this type of nonreciprocal change.
   (2) Increases in the gene copy number contribute to cancer transformation.
In sarcomas, the chromosome 12q13-14 region is commonly amplified.

(3) Extra copies of the ERBB2 (HER2/neu) gene cause overexpression of the epidermal growth factor protein, which is associated with aggressive breast cancer.

2. Nomenclature common to cytogenetic reports includes the modal number of chromosomes, the sex chromosome designation (XX or XY or aberrations of these chromosomes), the abnormality abbreviation, with the first chromosome separated with a semicolon from the second chromosome t(14;16), and then the arm and band number (q32; q23) (Table 5-1).

B. Gene expression (tumor) profiling uses multiple techniques (e.g., gene sequencing) to identify the expression (proteins) of tens to thousands of genes concurrently. It uses a personalized approach to cancer to diagnose, predict outcomes, or suggest the best treatment regimen for a person’s cancer. Techniques such as a DNA microarray or serial analysis of gene expression (SAGE) are also used.

1. Colon cancer profiling examples include OncotypeDX and ColoPrint.

2. Breast cancer gene profiling examples include Mammaprint, Symphony, and OncotypeDX.

3. Myeloma Prognostic Risk Signature (MyPRS) measures the expression values (levels) of 70 risk-related genes.

V. Potential therapeutic interventions

A. Pharmacogenomics and pharmacogenetics (Klotz, 2007)

1. Pharmacogenetics identifies the genetic basis for differences in the metabolism of an agent and associated treatment response, which can be used to individualize therapy.
a. A superfamily of enzymes, including the cytochrome P450 family, responsible for oxidation reactions for drug metabolism:

1. Root symbol: CYP
2. Arabic number for family
3. Letter for subfamily
4. Arabic numeral for specific gene
5. Number 1 followed by an asterisk (*) denotes the wild-type gene (most common)
6. Additional number with (*) signifies a variant (*5)
7. The enzyme (protein or gene product) identified as CYP2C19 and gene italicized (CYP2C19)
8. Variations in specific allele frequencies among different populations; for example, the variant CYP2D6*4 occurs frequently in whites, whereas Asians have a higher frequency of CYP2D6*10

b. Pharmacodynamics—study of the biochemical and physiologic effects of drugs on the body

c. Pharmacokinetics—description of how the body absorbs, distributes, metabolizes, and excretes a drug

d. Genetic variation—affects differences in efficacy, toxicity, pharmacodynamics, and pharmacokinetics

1. The DPD protein of the DYPD gene is involved in the metabolism of 5-fluorouracil (5-FU). DPD inactivates 80% of active 5-FU. Persons with a DYPD*2A variant have a greater risk of a grade 3 to 4 toxicity, most commonly neutropenia.

2. The enzyme TPMT regulates 6-mercaptopurine (6-MP) for acute lymphoblastic leukemia (ALL). Persons with low TPMT activity may have high concentrations of 6-MP, leading to toxicities. Dosages are based on types of variants with TPMT^*2, with TPMT^*3A having low or intermediate TPMT activity. TPMT^*1 (wild-type) has the highest TPMT activity, heterozygotes (^*1/^*3) with intermediate and (^*3/^*3) with the lowest activity.

3. Drug transporters are responsible for pumping drug molecules across cell membranes. If these transporters are overactive, interference with drug effectiveness will occur. One of the transporters, P-glycoprotein, is encoded by the ABCB1 gene. P-glycoprotein decreases intestinal absorption and brain...
uptake while increasing drug excretion via the biliary intestinal and renal systems. High activity of \( ABCB1 \) could increase removal of chemotherapy drugs, causing unsatisfactory treatment outcomes.

e. Phenotypic responses of genotype that affect response to active and prodrug responses (Table 5-2).

2. Pharmacogenomic testing (Table 5-3) includes the following:

<table>
<thead>
<tr>
<th>Genotype-Predicted Phenotype</th>
<th>Patient’s Gene Pair</th>
<th>Anticipated Impact on Active Drug</th>
<th>Anticipated Impact on Prodrug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor or slow metabolizer</td>
<td>Homozygous for both variants with absent or nonfunctioning protein</td>
<td>Decreased efficiency in converting active drug to inactive metabolites Increases risk for higher levels of active drug and clinical toxicity</td>
<td>Inability to convert inactive prodrug to active metabolites If prodrug has no therapeutic properties, then patient will experience lack of efficacy despite drug dose increases</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Heterozygous variant of one gene results in absent or nonfunctioning protein variant of other member of gene pair results in protein with reduced function -or- Pair of genes, each with variant that results in protein with reduced function -or- One member of gene pair with variant results in protein reduced function other allele has sequence consistent with full functioning protein</td>
<td>Decreased efficiency in converting active drug to inactive metabolites Increases risk for higher levels of active drug and clinical toxicity If drug is normally dosed low and slowly titrated upward, effectiveness may be achieved sooner than in extensive metabolizers</td>
<td>Decreased efficiency in converting inactive prodrug to active metabolites Decreased effectiveness at standard maintenance doses may be anticipated</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Homozygous with sequence for full-functioning protein</td>
<td>Active drug given at standard doses metabolized to inactive components, achieving effectiveness without or with minimal adverse drug reactions (ADRs)</td>
<td>Prodrug converted to active metabolites achieving effectiveness without or with minimal ADRs</td>
</tr>
<tr>
<td>Ultra-rapid metabolizer</td>
<td>Heterozygous with one locus consistent with full functioning protein, other locus has two or more copies of gene sequence resulting in full functioning protein</td>
<td>Increased efficiency in converting active drug to inactive metabolites Risk for decreased effectiveness at standard doses</td>
<td>Increased efficiency in converting prodrug to active metabolites Increased risk for toxicity from higher-than-expected levels of active metabolites</td>
</tr>
</tbody>
</table>

a. Genetic testing is required for some cancer therapies. See Table 5-4 for a list of some of these cancer treatment agents (Whirl-Carrillo et al., 2012).

b. Individualized treatment is based on the genetic characteristics of the individual and the tumor (see tumor profiling, section IV B, above) (Roses, 2000).

c. Testing for use of drugs is specifically aimed at individualized genetic change and altered protein product of tumors.
B. Proteomics
   1. Analysis of the structure, composition, and function of proteins
   2. Can aid in the diagnosis and enhance the understanding of the biologic basis of cancer

C. Somatic gene therapy
   1. Introduction of a functioning gene into the somatic cells to replace missing or defective genes or to provide a new cellular function
   2. Ongoing investigational trials using somatic gene therapy for a variety of cancers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Molecular Effect</th>
<th>Polymorphism (Nucleotide Translation)</th>
<th>Drug</th>
<th>Effect on Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytochrome P450 family</td>
<td>Decreased enzyme activity</td>
<td>Various polymorphism</td>
<td>Various</td>
<td>Interindividual variability in pharmacokinetics (PK)</td>
</tr>
<tr>
<td>TPMT2, 3A, 3C</td>
<td>Decreased enzyme activity</td>
<td>Various polymorphism</td>
<td>6-MP, thioguanine</td>
<td>Hematopoietic toxicity</td>
</tr>
<tr>
<td>UGT1A 28</td>
<td>Decreased enzyme activity</td>
<td>TA repeats in 5' promoter</td>
<td>Irinotecan</td>
<td>Neutropenia toxicity</td>
</tr>
<tr>
<td>MDR1</td>
<td>Low expression</td>
<td>(C3435T)</td>
<td>Various</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>TYMS</td>
<td>Increased enzyme activity</td>
<td>3 tandem repeats</td>
<td>5-FU, Methotrexate</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>DPYD</td>
<td>Decreased enzyme activity</td>
<td>IVS14 + 1G</td>
<td>5-FU, Methotrexate</td>
<td>Neutropenia toxicity</td>
</tr>
<tr>
<td>DHFR</td>
<td>Increasing enzyme activity</td>
<td>T91C</td>
<td>Methotrexate</td>
<td>Drug resistance</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Decreased enzyme activity</td>
<td>(C677T) (A1298C)</td>
<td>5-FU, Methotrexate</td>
<td>Toxicity</td>
</tr>
<tr>
<td>c-KIT</td>
<td>Constitutive signal activation</td>
<td>D860 N567K</td>
<td>Imatinib</td>
<td>Desensitizes activity in GIST</td>
</tr>
<tr>
<td>K-RAS</td>
<td>Inhibition of the tyrosine kinase domain-binding drug</td>
<td>G12x G13D</td>
<td>Cetuximab Panitumomab</td>
<td>Desensitizes activity in colon-rectum</td>
</tr>
<tr>
<td>B-RAF</td>
<td>Inhibition of the tyrosine kinase domain-binding drug</td>
<td>V600E</td>
<td>Vemurafenib Gefitinib</td>
<td>Good response in melanomas</td>
</tr>
<tr>
<td>EGFR</td>
<td>Inhibition of the tyrosine kinase domain-binding drug</td>
<td>L858R</td>
<td>Erlotinib</td>
<td>Good response in NSCLC</td>
</tr>
<tr>
<td>BCR/ABL fusion gene</td>
<td>Constitutive signal activation</td>
<td>T(9;22) BCR/ABL</td>
<td>Imatinib Dasatinib Nilotinib</td>
<td>Good response in CML</td>
</tr>
<tr>
<td>ABL</td>
<td>Inhibition of the tyrosine kinase domain-binding drug</td>
<td>T315I; M351T</td>
<td>Imatinib</td>
<td>Drug resistance in CML</td>
</tr>
<tr>
<td>PML/RARA fusion gene</td>
<td>Block of myeloid lineage cells</td>
<td>T(15;17) PML/RARA</td>
<td>All-Trans Retinoic acid (ATRA)</td>
<td>Good response in AML-M3 subtypes</td>
</tr>
<tr>
<td>ADRB1</td>
<td>G-protein altered</td>
<td>R389G</td>
<td>Beta-blockers</td>
<td>Desensitizes activity</td>
</tr>
<tr>
<td>MHC class B1</td>
<td>HLA-B~5701 haplotype</td>
<td>Several SNPs including codon K751Q</td>
<td>Abacavir</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Associated with a higher/ lower warfarin dose</td>
<td>Many, VKORC1 haplotypes including codon G3673A</td>
<td>Warfarin</td>
<td>Variable anticoagulant effect</td>
</tr>
</tbody>
</table>

5-FU, 5-Fluorouracil; 6-MP, 6-mercaptopurine; ADRB, adrenergic beta-receptors; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; DHFR, dihydrofolate reductase; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; MDR1, multidrug resistance 1; MTHFR, 5,10-methylene tetrahydrofolate reductase; NSCLC, non–small-cell lung cancer; PK, pharmacokinetics; TPMT, thiopurine methyl transferase; TYMS, thymidylate synthase; UGT1A1, UDP-glucuronosyl transferase 1A1; VKORC1, vitamin K epoxide reductase complex 1.

*The present list is not comprehensive.

†Genes are available for genotyping test or under consideration for clinical diagnostics.

Adapted from Di Francia, R., Valente, D., Catapano, O., Rapolo, M., Tirelli, U., & Berretta, M. (2012). Knowledge and skills needs for health professions about pharmacogenomics testing field. European Review for Medical and Pharmacological Sciences, 16(6), 781–788.
D. Germline gene therapy

1. Introduction of a functioning gene into the egg or sperm to prevent transmission of a genetic mutation
2. Germline gene therapy not available because it raises several ethical, legal, and social concerns

VI. Common hereditary cancer syndromes and cancer susceptibility genes

A. The common hereditary cancer syndromes, clinical manifestations, inheritance patterns, and genes are outlined in Table 5-5.
B. Features of hereditary cancer (Lindor, McMaster, Lindor & Greene, 2008)

1. Family member with a known germline deleterious mutation in a cancer susceptibility gene
2. Early age of cancer onset
3. Cancer of rare histology
4. Cancer in two or more close biologically related relatives
5. Bilateral cancer in paired organs (e.g., breast or ovary)
6. Multiple primary cancers in a single individual
7. Constellation of cancers in the family part of a known hereditary cancer syndrome

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**Table 5-4**

<table>
<thead>
<tr>
<th>Pharmacogenetic Biomarker</th>
<th>Cancer Target</th>
<th>Oncologic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Required Prior to Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF (cobas 4800 BRAF V600 Mutation Test)</td>
<td>Unresectable or metastatic melanoma</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>EGFR expression</td>
<td>Metastatic colon cancer, Head and neck (testing not required) cancer</td>
<td>Cetuximab Panitumumab</td>
</tr>
<tr>
<td>Estrogen receptor (ER) and progesterone receptor (PR)</td>
<td>Breast cancer</td>
<td>Exemestane Fulvestrant Letrozole</td>
</tr>
<tr>
<td>(K)-ras</td>
<td>Colon cancer</td>
<td>Cetuximab Panitumumab Dasatinib</td>
</tr>
<tr>
<td>HER2/neu overexpression</td>
<td>Breast cancer</td>
<td>Trastuzumab Lapatinib</td>
</tr>
<tr>
<td>Presence of Philadelphia chromosome (Ph+)</td>
<td>Chronic myeloid leukemia (CML)</td>
<td>Imatinib Imatinib</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>Gastrointestinal stromal tumors (GIST)</td>
<td>Tyrosine kinase inhibitors</td>
</tr>
<tr>
<td>FIP1L1-PDGFRα</td>
<td>Myelodysplastic/proliferative disorders</td>
<td>Imatinib</td>
</tr>
<tr>
<td><strong>Tests Recommended for Treatment Decision</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>NSCLC</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>G6PD</td>
<td>Tumor lysis syndrome</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>Ph+</td>
<td>CML</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>TPMT variants</td>
<td>Acute lymphocytic leukemia, acute nonlymphocytic leukemia</td>
<td>Mercaptopurine, thioguanine</td>
</tr>
<tr>
<td>UGT1A1 variants</td>
<td>Colorectal cancer</td>
<td>Irinotecan Nilotinib</td>
</tr>
<tr>
<td><strong>Tests for Information Only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD-30</td>
<td>Hodgkin lymphoma Anaplastic large cell lymphoma</td>
<td>Brentuximab vedotin</td>
</tr>
<tr>
<td>c-Kit expression</td>
<td>Kit+ gastrointestinal stromal tumors</td>
<td>Imatinib</td>
</tr>
<tr>
<td>DYPD deficiency</td>
<td>Colorectal or breast cancers</td>
<td>Capecitabine, 5-fluorouracil</td>
</tr>
<tr>
<td>Philadelphia chromosome deficiency (Ph-)</td>
<td>CML</td>
<td>Busulfan</td>
</tr>
<tr>
<td>PML/RAR gene expression</td>
<td>Promyelocytic leukemia</td>
<td>Arsenic Trioxide</td>
</tr>
</tbody>
</table>

*This information changes frequently and should be checked for current accuracy.

Table 5-5

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical Manifestations</th>
<th>Gene</th>
<th>Mode of Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Cerebral ataxia, oculocutaneous telangiectasias, radiation hypersensitivity, leukemia, lymphoma, breast cancer, and other solid tumors</td>
<td>ATM</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Basal cell nevus syndrome</td>
<td>Basal cell carcinoma, medulloblastoma, ovarian fibrosarcoma, odontogenic keratocyst, palmar or plantar pits, and ectopic calcification</td>
<td>PTCH</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Breast/ovarian cancer syndrome</td>
<td>Breast, ovary, fallopian tube, prostate, pancreas, and possibly gastric as well as other sites</td>
<td>BRCA1</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>Multiple mucocutaneous lesions, vitiligo, angiomomas, benign proliferative disease of multiple organ systems, macrocephaly, breast cancer, thyroid (nonmedullary) cancer, endometrial cancer, and renal cancer, as well as other possible sites</td>
<td>PTEN</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Colon polyposis (adenomas), desmoid tumors, osteomas, thyroid cancer, and hepatoblastoma</td>
<td>APC</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Familial juvenile polyposis</td>
<td>Hamartomatous polyps of the stomach, small intestine, colon, and rectum Colon cancer as well as cancers of the stomach, duodenum, and pancreas</td>
<td>BRIP1A/SMA4</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>Leukemia, hepatocellular carcinomas, squamous cell carcinomas of the head and neck, esophagus, cervix, vulva, anus, hepatic adenoma, myelodysplastic syndrome, aplastic anemia</td>
<td>FANCA/FANCM/FAAP95/FANCC/FANCD1/FANCA2/FANCD2/FANCDF/FANCF/FANCG/XRCC/FANCI/BACH1/BRIP1/FANCL/HF9/FAPA43/PDG/FANCM/FAAP250/Hef/FANCCN/PALB2</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Basal cell carcinoma, brain tumors, and ovarian cancer</td>
<td>PTCH</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer [HNPCC])</td>
<td>Cancers of the colon, rectum, stomach, small intestine, biliary tract, brain, endometrium and ovary, and transitional cell carcinoma of the ureters and renal pelvis</td>
<td>MLH1/MSH2/MSH6/MSH3/MSH1/MSH2</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Breast cancer, sarcoma, brain tumors, leukemia, and adrenocortical carcinoma, as well as other possible cancers</td>
<td>TP53</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma, astrocytoma, pancreatic cancer, and ocular melanoma, as well as possibly breast cancer</td>
<td>CDKN2A/CDK4</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Muir-Torre syndrome</td>
<td>Gastrointestinal and genitourinary cancers, skin, breast cancer, and benign breast tumors</td>
<td>MSH2/MLH1</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 1</td>
<td>Pancreatic and neuroendocrine tumors, gastrinomas, insulinomas, parathyroid disease, and carcinoids, as well as adrenal cortical tumors, malignant schwannomas, ovarian tumors, pancreatic islet cell cancers, and gastrointestinal stromal tumors</td>
<td>MEN1</td>
<td>Autosomal dominant</td>
</tr>
</tbody>
</table>

Continued
C. Indications for cancer predisposition testing

1. Criteria for predisposition genetic testing vary, depending on the suspected inherited cancer syndrome and mutations in the gene or genes associated with that syndrome
   a. Universal criteria for predisposition genetic testing include the following:
      1. Confirmed family history consistent with the hereditary cancer syndrome
      2. A test that can be interpreted once performed
      3. The test that will be used to assist in medical decision making or will assist in diagnosis of a condition

---

### Table 5-5

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical Manifestations</th>
<th>Gene(s)</th>
<th>Mode of Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td>Medullary thyroid cancer, pheochromocytoma, papillary thyroid cancer, and ganglioneuromas</td>
<td>RET</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>MYH-associated polyposis (MAP)</td>
<td>Colon cancer and duodenal cancer, as well as colon, duodenal, and gastric fundic gland polyps, osteomas, sebaceous gland adenomas, and pilomatrixomas</td>
<td>MYH</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Malignant peripheral neural sheath tumors, neurofibromas, benign pheochromocytomas, meningiomas, hamartomatous intestinal polyps, gastrointestinal stromal tumors, optic gliomas, café-au-lait macules, axillary or inguinal freckles, iris hamartomas, and sphenoid wing dysplasia or congenital bowing or thinning of long bones, as well as other malignancies</td>
<td>NF1</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>Neurofibromas, gliomas, vestibular schwannoma, schwannomas of other cranial and peripheral nerves, meningioma, ependymomas, and astrocytoma</td>
<td>NF2</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Prostate and other cancers not established</td>
<td>BRCA1, BRCA2</td>
<td>Varied: autosomal dominant, autosomal recessive, X-Linked</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Retinoblastoma, soft tissue sarcoma and osteosarcoma, melanoma, brain tumors, nasal cavity cancers, lung cancer, bladder cancer, retinomas, and lipomas</td>
<td>RB1</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Von Hippel-Lindau</td>
<td>Renal cell cancer, hemangioblastoma of brain, spinal cord, and retina, renal cysts, pheochromocytomas, endolymphatic sac tumors, and pancreatic islet cell tumors</td>
<td>VHL</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>Wilm tumor and nephrogenic rests</td>
<td>WT1</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>Basal and squamous cell skin cancer, melanoma, and sarcoma, as well as brain, lung, breast, uterus, kidney, and testicle cancers, leukemia, conjunctival papillomas, actinic keratosis, lid epithiomas, keratoacanthomas, angiomas, fibromas</td>
<td>XPA, ERCC3, XPC, ERCC2, DDB2, ERCC4, ERCC5, POLH</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>

(4) Informed consent by the client to be tested
(a) The National Society of Genetic Counselors defines genetic counseling as “the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease (National Society of Genetic Counselors’ Definition Task Force, 2006).
(b) Providers delivering genetic counseling may be physicians, nurses, or genetics counselors with specialized training in genetics. Table 5-6 summarizes some resources available for finding a health care provider trained in genetics.

2. The American Society of Clinical Oncology (ASCO) also recommends a review of the evidence of clinical utility for any genetic test (including multiplex tests, tests for low or moderate disease genes, and SNP tests) be considered when either ordering or making medical recommendations based on a test result (Robson et al., 2010).

3. Not every client is appropriate for predisposition genetic testing for inherited cancer susceptibility.
   a. Genetic tests, including those for cancer risk, are also available directly to the consumer, in which case ASCO also recommends a review of the clinical utility of the result before making medical recommendations (Robson et al., 2010).

D. Outcomes for cancer predisposition testing
1. The predictive value of a negative test result varies, depending on whether a known genetic mutation exists in the family.
   a. A negative test result in the presence of a known genetic mutation indicates that the client is within the general population risk of cancer associated with that branch of the family.
      (1) However, family history from the other parent still influences the risk of developing cancer.
   b. A negative result with no known family genetic mutation may occur because of one of the following:
      (1) Identifying a mutation in a cancer susceptibility gene may not be possible because of the limited sensitivity of the techniques used.
      (2) The function of the gene may be affected by a mutation in a different gene.
      (3) The cancer in the family may be associated with a cancer susceptibility gene other than the one tested.
      (4) The cancer in the family is not the result of a germline genetic mutation.
   c. A mutation of uncertain clinical significance is identified. This refers to mutations in which the association with cancer risk cannot be established.
2. The predictive value of a positive test result varies, depending on the type of genetic mutation identified and the degree of certainty that the function of the gene has been affected.
   a. Penetrance refers to the proportion of all individuals with a specific genotype that express the specific trait such as cancer.
   b. Expression refers to the degree to which a single individual with a specific genotype will exhibit a specific trait (e.g., cancer).
      (1) Expression may be different for different genetic mutations in the same cancer susceptibility gene.
      (2) Expression may also be affected by other genetic variations as well as by the environment and other personal factors.

VII. Medical management issues associated with the care of individuals harboring a mutation in a cancer susceptibility gene
A. The management of cancer risk falls into five basic categories:

| Table 5-6 |
| Resources for Finding a Genetic Health Care Provider |

<table>
<thead>
<tr>
<th>Resource</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society of Human Genetics</td>
<td><a href="http://www.ashg.org/">http://www.ashg.org/</a></td>
</tr>
<tr>
<td>International Society of Nurses in Genetics</td>
<td><a href="http://www.isong.org/">http://www.isong.org/</a></td>
</tr>
</tbody>
</table>
1. Surveillance, which is monitoring to detect cancer as early as possible, when the chances for cure are greatest.
2. Risk-reducing surgery (also called prophylactic surgery), which is the removal of as much of the tissue at risk as possible to reduce the risk of developing a cancer.
3. Chemoprevention, which involves taking a medicine, vitamin, or other substance to reduce the risk of cancer.
4. Risk avoidance, which is the avoidance of exposures that may increase the risk of certain cancers.
5. Healthy behaviors, including diet and exercise.

B. Cancer risk management strategies available to individuals at high risk for cancer because of a mutation in a cancer susceptibility gene vary according to the gene, specific gene mutation identified, or both. Each strategy has varying degrees of risks, benefits, and limitations, as well as varying levels of evidence supporting the specific intervention.

1. The National Cancer Institute Physician Data Query (PDQ) Cancer Information Summaries on Genetics at http://www.cancer.gov/cancertopics/pdq/genetics provide evidence-based reviews for many common cancer genetic syndromes and include a summary of cancer risk management strategies associated with that particular syndrome, as well as the associated levels of evidence.

VIII. Ethical, legal, and social issues associated with genetic information (Offit & Thom, 2007)

A. Predisposition genetic testing may have psychological consequences, some of which could impact subsequent health behaviors and family communication.

1. Survivor guilt is often observed in persons who have not inherited the genetic mutation that is present in other close family members.
2. Transmitter guilt is often observed when family members pass on the genetic mutation to one of their offspring.
3. Heightened anxiety may result when clients learn that they are at a substantially increased risk for developing cancer or another primary lesion.
4. Depression and anger may occur regardless of genetic status.
5. Personal identity issues result because genetic information involves the very essence of an individual.
6. Regret for previous decisions may be present in clients who have made major decisions based on their perceived cancer risk, and testing results are inconsistent with what they had previously thought.
7. Uncertainty occurs because predisposition genetic testing does not provide information about if or when cancer develops. In many instances, no proven risk-reducing strategy exists.
8. Intrafamilial issues arise because predisposition genetic testing affects all family members. These issues include, but are not limited to, the following:
   a. Coercion regarding testing, disclosure of testing results to family members, and cancer risk management approaches.
   b. Effect of the genetic information on the partner, who is not at risk physically but whose children may be impacted.
9. Stigmatization both within the family and within the individual’s social network.
10. Identification of an incidental finding if multiplex testing or some form of whole genome analysis (e.g., whole exome sequencing, whole genome sequencing) is performed.

B. Predisposition genetic testing also has social implications.

1. Financial considerations
   a. Predisposition genetic testing may be very expensive. Some, but not all, insurers cover testing and counseling.
   b. Insurers may be reluctant to cover enhanced surveillance programs unless efficacy has been proven.
   c. Insurers may not be willing to cover the expense of prophylactic surgery unless it has proven benefit.
2. Quality assurance of laboratory testing is not certain because no regulation exists beyond approval for molecular laboratories that perform testing based on the CLIA.
3. Availability and quality assurance of genetic counseling are of concern, given the small number of trained providers in cancer genetics.

C. Legal issues for the client undergoing predisposition testing may involve the following:

1. Discrimination may occur for those harboring an altered cancer susceptibility gene because they may be considered as having a preexisting condition or may be too high a risk to insure or employ (Offit & Thom, 2007).
   a. Health insurance
   b. Life insurance
   c. Disability insurance
   d. Long-term care insurance
   e. Education
   f. Employment
2. State and federal legislative approaches have already been proposed or enacted, depending on the issue and state (National Cancer Institute PDQ Genetics Editorial Board, 2013).

a. The Health Insurance Portability and Accountability Act (HIPAA), a federal law enacted in 1996, states that genetic information cannot be used as a pre-existing condition or to determine eligibility for insurance.
   (1) This protection only applies to group and self-funded plans.
   (2) This law does not protect against rate hikes, access of insurers to an individual’s genetic information, or the insurer requiring genetic testing as a condition of insurance coverage.

   (1) Health insurance protections include protections against accessing an individual’s genomic information, requirements for an individual to undergo a genetic or genomic test, and using genomic information against a person during medical underwriting.
   (2) Employment protections include prohibiting employers from accessing an individual’s genetic information, use of genomic information to deny employment, or collecting genomic information without consent.
   (3) The GINA does not supersede state legislation that provides for more extensive protections.
   (4) The GINA does not apply to active duty military personnel, Veterans Administration, or the Indian Health Service because the laws amended for GINA do not apply to these groups.

c. The U.S. Equal Employment Opportunity Commission released guidelines in March 1995 on the definition of “disability” under the Americans with Disabilities Act (ADA), which is now extended to include discrimination based on genetic information. This set of guidelines is not law but simply is an interpretation of the language of the ADA and may be overturned in a court of law.

3. Self-insured employers may also be exempt from state laws and regulations on health insurance because of the Employee Retirement Income Security Act of 1974 (ERISA), which governs employer pension plans as well as other benefits.

D. Informed consent should precede genetic testing and include the following (Riley et al., 2012; Weitzel, Blazer, Macdonald, Culver, & Offit, 2011):
   1. Purpose of the genetic test
   2. Motivation for testing
   3. Risks of genetic testing
   4. Benefits of genetic testing
   5. Limitations of genetic testing
   6. Inheritance pattern of the gene(s) being tested
   7. Risk of misidentified paternity, if applicable
   8. Accuracy and sensitivity of genetic testing method
   9. Outcomes of genetic testing
   10. Confidentiality of genetic testing results
   11. Possibility of discrimination
   12. Alternatives to genetic testing
   13. How testing will impact health care decision making
   14. Cost of testing
   15. Right to refuse
   16. Testing in children (<18 years of age)
      a. Performed when clinical utility for testing in children has been established
   17. Management of incidental findings

E. Genetic technology raises legal liability issues for the health care provider.
   1. Privacy and confidentiality
      a. Genetic information of all types should be handled in a confidential manner to prevent unauthorized access.
   2. Genetic testing should be preceded by genetic counseling by a genetic health care professional, education, counseling, and informed consent.
   3. Health care providers may have a duty to inform clients regarding their potential for increased cancer risk from an inherited susceptibility and the availability of predisposition genetic testing (Offit, Groeger, Turner, Wadsworth, & Weiser, 2004).

F. Table 5-7 summarizes some available genetic and genomic resources.

NURSING IMPLICATIONS

I. Interventions to assist the client and family to understand cancer genetics and genetic testing
   A. Description of the organization and function of genetic material and the role of genetics in carcinogenesis
Table 5-7
Genomic Health Care Resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential Genetic and Genomic Competencies for Nurses with Graduate Degrees</td>
<td><a href="http://nursingworld.org/MainMenuCategories/EthicsStandards/Genetics-1/Essential-Genetic-and-Genomic-Competencies-for-Nurses-With-Graduate-Degrees.pdf">http://nursingworld.org/MainMenuCategories/EthicsStandards/Genetics-1/Essential-Genetic-and-Genomic-Competencies-for-Nurses-With-Graduate-Degrees.pdf</a></td>
</tr>
<tr>
<td>Genomics Community for Education (G2C2)</td>
<td><a href="http://www.g-2-c-2.org">http://www.g-2-c-2.org</a></td>
</tr>
<tr>
<td>Global Genetics and Genomics Community</td>
<td><a href="http://www.g-3-c.org">http://www.g-3-c.org</a></td>
</tr>
<tr>
<td>National Cancer Institute Physician Data Query (PDQ) Cancer Information Summaries: Genetics</td>
<td><a href="http://cancertopics.pdq/genetics">http://cancertopics.pdq/genetics</a></td>
</tr>
<tr>
<td>Online Mendelian Inheritance in Man</td>
<td><a href="http://www.omim.org/">http://www.omim.org/</a></td>
</tr>
<tr>
<td>Oncology Nursing Society. (2012). Oncology nursing: The application of cancer genetics and genomics throughout the oncology care continuum</td>
<td><a href="http://www.ons.org/Publications/Positions/HealthCarePolicy">http://www.ons.org/Publications/Positions/HealthCarePolicy</a></td>
</tr>
<tr>
<td>Pharmacogenomics Education Program (PharmGenEd)</td>
<td><a href="https://pharmacogenomics.ucsd.edu/">https://pharmacogenomics.ucsd.edu/</a></td>
</tr>
<tr>
<td>U.S. Surgeon General’s Family History Initiative</td>
<td><a href="http://www.hhs.gov/familyhistory/">http://www.hhs.gov/familyhistory/</a></td>
</tr>
</tbody>
</table>

B. Assessment of the client’s beliefs about the cause of cancer in the family and correct misconceptions
C. Description of the process for cancer risk evaluation and predisposition genetic testing
D. Discussion of the risks and benefits of predisposition genetic testing
E. Discussion of the risks and benefits of pharmacogenetic or genomic testing
F. Description of the rationale for the use of tumor profiling

II. Interventions to decrease perceived and actual barriers to cancer risk management
A. Education and monitoring of the performance of self-examination techniques
B. Education on the benefits of cancer risk management
C. Facilitating reimbursement for cancer risk management procedures
D. Encouragement of communication regarding fears and concerns

III. Interventions to enhance coping and adaptation
A. Referral of the client, family, or both to community support services.
B. Referral of the client, family, or both to professional counseling services, when indicated
C. Encouragement of the use of coping strategies that have previously been effective

References


