GENETICS: ETIOLOGY OF SPORADIC AND HEREDITARY CANCERS

Goal:
The goal of this module is to improve recognition of familial cancer syndromes so that appropriate patient management strategies can be implemented.

After completing this activity participants will be able to:
• Define oncogenes, tumor suppressors, and DNA repair genes
• Explain how oncogenes, tumor suppressors, and DNA repair genes contribute to cancer development
• Differentiate between sporadic and hereditary cancers
• Identify patients at risk for hereditary cancer syndrome
• Obtain a cancer family history
• Locate patient management recommendations, educational materials, and support resources

Professional Practice Gaps
In an effort to define what healthcare providers need to know about medical genetics, several organizations developed core competencies (NCHPEG, 2000; ASHG, 2001). However, because clinical genetics is a relatively young and evolving field of medicine, many practitioners received insufficient formal genetics education. As a result, they express a lack of confidence in their clinical genetics knowledge and a lack of confidence in their ability to provide genetic counseling.

THE PREVALENCE OF CANCER

Cancer is an extremely common disease in the United States. Men in the United States have a lifetime risk of slightly less than 50%, and women in the United States have slightly less than a 33% lifetime risk for some form of cancer (American Cancer Society 2009). These risk figures translate into an estimated 1,479,350 new cancer cases during the year 2009.

The most common forms of cancer are illustrated below. Cancers are listed in descending order of frequency of new cancer cases.

The majority of cancers occur sporadically, although 5% to 10% of cancers are heritable
(American Cancer Society 2009). For those individuals who inherit a genetic predisposition for cancer, the risk of developing cancer is increased compared to general population risk(s). All cancer, whether occurring as part of a cancer syndrome or as an isolated case, develops in a similar multi-step process.

CANCER BASICS

Normal Cell Growth
All cancer is the result of abnormal cell growth and division. Because cell growth is such an important process, it is carefully regulated by numerous cellular components. Some components act to promote cell growth while others act to prevent it. A healthy cell maintains a balance between growing too quickly and not growing at all.

The illustration below depicts a healthy cell receiving an external message to grow. The message is received at the cell membrane by a receptor. The receptor then signals enzymes inside the cell to promote regulated growth.

Image from NCI, Understanding Cancer Series: Cancer
CELL DIVISION

During the cell growth process, there are many checkpoints in place to help ensure that only normally functioning cells grow and reproduce themselves. The majority of human body cells (somatic cells) reproduce through a process called mitosis. Sperm and egg cell precursors (germline cells) replicate through a process known as meiosis. Diagrams of both mitosis and meiosis are displayed below.

ABNORMAL CELL GROWTH

If the balance is shifted in favor of the growth promoters or if the cell checkpoints are lost, then cell growth may proceed at a more rapid pace and/or cells may behave abnormally. Over time, abnormal
cells may reproduce, creating a mass of cells, or tumors. Tumors are categorized as either benign or malignant. Benign tumors are slow growing and are usually enclosed in a fibrous capsule so that they do not spread to other body parts. Benign tumors are not cancer. Malignant tumors, however, tend to grow quickly and have the potential to spread to other tissues and areas of the body. Malignant tumors are considered cancerous.

The illustration below demonstrates the difference between normal cell growth and abnormal cell growth. Normal cells grow at a rate that allows for cells to proceed through checkpoints. Any cell that has been damaged is either repaired or directed to undergo programmed cell death, or apoptosis. Apoptosis prevents unrepaird cells from replicating. In contrast to healthy cells, cancerous cells tend to grow at a faster pace, and the damaged cells escape from apoptosis.

![Image from NCI, Understanding Cancer Series: Cancer]

**BENIGN TUMORS**
- Grow slowly
- Do not spread
- Are not cancer

**MALIGNANT TUMORS**
- Grow rapidly
- Spread
- Are cancerous
CHARACTERISTICS OF CANCER CELLS

In addition to abnormal cell growth patterns, cancer cells also have numerous other differences when compared to normal cells. Cancerous cells may demonstrate changes in appearance, biochemistry, and function. The table below illustrates some common differences.

![Microscopic Appearance of Cancer Cells](image)

Image from NCI, *Understanding Cancer Series: Cancer*

CATEGORIES OF CANCER

Cancers can be subdivided into 3 main groups:

- Carcinomas
- Leukemias and lymphomas
- Sarcomas

Within each of the 3 major groups, tumors are further classified by site, tissue type, histological appearance, and degree of malignancy.

<table>
<thead>
<tr>
<th>Carcinomas: Carcinomas are cancers that occur either in the epithelial cells covering the surface of the body or in epithelial cells lining the internal organs (intestines, bronchi, etc.) (tissues arising from the embryonic endoderm and ectoderm). They are the most common of all cancers</th>
<th>Examples: Kidney cancer Melanoma</th>
</tr>
</thead>
</table>
Leukemias and Lymphomas: These are cancers that occur in the circulatory or lymphatic system (tissues arising from the embryonic mesoderm). They are the second most common type of cancer (approximately 8%).

Sarcomas: Sarcomas are tumors that occur in connective tissue (tissues arising from the embryonic mesoderm layer). They are the rarest form of neoplasm (approximately 1%-2%).

**CANCER GENES**

**Introduction to Genes Involved in Cancer**
All cancers are caused by mutations in genes participating in cell growth and division. For convenience, these genes are often classified into 3 categories: oncogenes, tumor suppressors, and DNA repair genes.

**Oncogenes:** Oncogenes normally function as proto-oncogenes to promote normal cell growth. A deleterious mutation in a proto-oncogene causes the gene to be renamed as an oncogene. Oncogenes cause cancer by becoming more active or gaining an additional function relative to their proto-oncogene counterpart.

**Tumor Suppressor Genes:** Tumor suppressor genes normally function to negatively regulate the cell growth and division process. A mutation in a tumor suppressor gene causes cancer by reducing the gene's normal activity or eliminating its function entirely.

**DNA Repair Genes:** DNA repair genes are responsible for double-checking and, if necessary, repairing genetic information. A mutation in a DNA repair gene may allow inaccurate genetic information to be replicated and passed on to daughter cells. Mutations in DNA repair genes lead to cancer by allowing mutations in the genome, including mutations in proto-oncogenes and tumor suppressors, to accumulate, disrupting normal cell growth and division.

**TUMOR SUPPRESSORS**
A second category of genes involved in carcinogenesis is tumor suppressors (sometimes referred to as gatekeepers). Properly functioning tumor suppressors negatively regulate the cell growth process by coordinating the timing of the cell cycle. Tumor suppressors can also direct cells to undergo apoptosis. This category of genes acts in opposition to proto-oncogenes, which positively regulate
cell growth. The 2 groups of genes together influence the cellular machinery so that the proper balance between growth and no growth is achieved.

A mutation in a tumor suppressor gene reduces the gene's normal activity or may eliminate its function entirely. Tumor suppressor genes behave in a recessive manner at the cellular level. If one member of a pair of tumor suppressor genes has a mutation in it, the remaining copy still functions and the cell growth process continues normally. If another mutation occurs on the remaining functional copy of the tumor suppressor gene, the inhibitory function of that gene is lost from the cell. At that point, cell growth may either speed up or damaged cells may no longer be able to initiate apoptosis.

Example: The tumor suppressor gene MEN1 codes for a gene product (protein) that is thought to have several different functions. Not all of the protein’s functions are well understood; however, the protein is known to be located predominantly in the nucleus of
the cell (Marsh and Zori, 2002). It is thought that MEN1 normally acts to slow cell growth by limiting transcription activity. In other words, MEN1 is thought to limit the ability of a cell to produce RNA from DNA, which in turn limits the amount of gene product (protein) a cell can produce.

In situations where both copies of MEN1 have mutations in them, the MEN1 protein can no longer perform its normal function. Cells are able to speed up gene product production and their growth rate, contributing to the development of cancer. People with 2 copies of nonfunctioning MEN1 genes are at increased risk to develop endocrine tumors.


DNA REPAIR GENES

The third category of genes involved in carcinogenesis is DNA repair genes (sometimes referred to as caretaker genes). Mutations in both proto-oncogenes and tumor suppressors contribute to cancer development through increased cell growth. Mutations in DNA repair genes allow cells with genetic damage to multiply. These mutations indirectly contribute to cancer formation through rapid cell growth as well.

In normally functioning cells, DNA repair genes double-check the genome to minimize any errors either introduced during DNA replication or as the result of environmental mutagens. If a DNA repair gene no longer functions, then cells with replication errors/mutations are allowed to grow and divide. Eventually, mutations may occur in either tumor suppressor genes or in proto-oncogenes, allowing for uncontrolled growth of cells harboring genetic mutations.

DNA repair genes act in a recessive manner at the cellular level. If one member of a pair of DNA repair genes has a mutation in it, the remaining copy still functions and the DNA repair process continues normally. If another mutation occurs on the remaining functional copy of the DNA repair gene, the repair function of that gene is lost from the cell.

The illustration below demonstrates the difference between a cell with a functioning DNA repair system and one with a malfunctioning repair system. Cells without working DNA repair systems are much more likely to become cancerous.
Example: One gene, hMLH1, normally produces a protein that functions as part of the cell's mismatch repair mechanism (U.S. National Library of Medicine 2013). The hMLH1 protein examines DNA for errors that occurred when the DNA was being copied for cell division. Each cell must faithfully copy its DNA so that upon cell division the new daughter cell will have all of the genetic information it needs to function. If an error in the copying process is found, the hMLH1 gene product will attempt to repair the problem. Normal function of the hMLH1 protein contributes to good cellular health. However, if the hMLH1 genes have mutations in both copies and the protein can no longer perform its job, daughter cells will be produced containing DNA with errors (mutations) in them. As more mutations accumulate in daughter cells, a greater number of genes will be negatively impacted. Eventually tumor suppressor and proto-oncogenes may be affected, allowing cell growth to speed up. People with 2 copies of inactive hMLH1 are at increased risk for cancer, especially colon cancer.

SPORADIC CANCERS

Of all cancers, 90% to 95% are sporadic. In other words, even though all cancers are caused by damage to genetic information, most cancers are not passed on from parent to child. Sporadic cancers develop as people acquire mutations in proto-oncogenes, tumor suppressor genes, and DNA repair genes. These mutations either occur in somatic cells or in germline cells that are not involved
in fertilization; therefore, the mutations are not passed on to the next generation. Acquired mutations accumulate over a person's lifetime. They are usually caused by chance events, including exposures to a variety of genetically damaging agents or as a result of errors in DNA replication prior to cell division.

**Clinical Example:** Todd is a 53-year-old Caucasian male. He is married and has 2 daughters and a son. Todd grew up on the coast of Florida. As a child, he enjoyed many outdoor activities including swimming, canoeing, and fishing. Todd continued to enjoy the warm, sunny climate in Florida as a teenager and young adult. Although Todd has fair skin and freckles, he always liked to maintain as much of a tan as possible and didn't often use sunblock. Recently, Todd noticed a new and unusual-looking mole on his arm, so he made an appointment with his family doctor. The mole looked suspicious to the physician, so he removed it and forwarded a sample to the laboratory for diagnosis. Shortly thereafter, Todd was diagnosed with basal cell carcinoma (the most common form of skin cancer) and was successfully treated. He now uses sunblock and protective clothing when outdoors. Todd's skin cancer was the result of sun damage. It was not a form of skin cancer that is considered to be part of a hereditary skin cancer syndrome.

![Todd's Family History](image)
Sporadic cancers are caused by a number of environmental agents, including chemicals, radiation, and biological agents that damage DNA. There are relatively few carcinogenic radiation exposures and biological agents compared to the number of chemical carcinogens.

The table below lists known carcinogens as well as the type of cancer(s) associated with each. (Note: This list is not all-inclusive.) Much of the content for this table was constructed from the federally maintained Report on Carcinogens.

<table>
<thead>
<tr>
<th>Chemical Carcinogens</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Oral cavity/pharynx, larynx, esophagus, liver</td>
</tr>
<tr>
<td>Aflatoxins (moldy peanuts)</td>
<td>Liver</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Skin, lung, liver</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Bronchus, lung, pleura</td>
</tr>
<tr>
<td>Auramine (dye workers)</td>
<td>Bladder</td>
</tr>
<tr>
<td>Azathioprine (immunosuppressant)</td>
<td>Non-Hodgkin's lymphoma, skin, liver</td>
</tr>
<tr>
<td>Benzene</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Benzidine (dye, rubber workers)</td>
<td>Bladder</td>
</tr>
<tr>
<td>Beryllium/beryllium compounds (metal workers)</td>
<td>Lung</td>
</tr>
<tr>
<td>1, 3-Butadiene (rubber manufacturing,</td>
<td>Lymphatic/hematopoietic</td>
</tr>
<tr>
<td>Chemical/Group</td>
<td>Cancer Sites</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Fungicides</td>
<td></td>
</tr>
<tr>
<td>1, 4-Butanediol dimethylsulfonate (Myleran) (chemotherapy)</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Cadmium/cadmium compounds (metal workers)</td>
<td>Lung, prostate, renal, bladder</td>
</tr>
<tr>
<td>Chlorambucil (immunosuppressant, chemotherapy)</td>
<td>Leukemia</td>
</tr>
<tr>
<td>1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNU) (chemotherapy)</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Bis (chloromethyl) ether and technical-grade chloromethyl methyl ether</td>
<td>Lung</td>
</tr>
<tr>
<td>Chromium (metal workers)</td>
<td>Lung</td>
</tr>
<tr>
<td>Coal tar pitches</td>
<td>Skin, scrotal, bladder</td>
</tr>
<tr>
<td>Coke oven emissions</td>
<td>Lung</td>
</tr>
<tr>
<td>Cyclophosphamide (immunosuppressant, chemotherapy)</td>
<td>Bladder, leukemia</td>
</tr>
<tr>
<td>Cyclosporin A (immunosuppressant)</td>
<td>Lymphoma, skin</td>
</tr>
<tr>
<td>Diethylstilbestrol (hormone)</td>
<td>Vaginal, cervical</td>
</tr>
<tr>
<td>Dioxin (2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD))</td>
<td>All cancers, especially lung and non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Erionite (manufacturing)</td>
<td>Lung, pleural</td>
</tr>
<tr>
<td>Ethylene oxide (alkylating agent)</td>
<td>Lymphatic/hemopoietic</td>
</tr>
<tr>
<td>Melphalan (chemotherapy)</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Methoxsalen with ultraviolet A therapy (PUVA) (psoriasis and vitiligo treatment)</td>
<td>Skin</td>
</tr>
<tr>
<td>Mineral oils (untreated and mildly treated)</td>
<td>Scrotal, skin, rectal, colon, lung, buccal, pharynx</td>
</tr>
<tr>
<td>Mustard gas</td>
<td>Respiratory tract</td>
</tr>
<tr>
<td>2-Naphthylamine (dye, rubber workers)</td>
<td>Bladder</td>
</tr>
<tr>
<td>Nickel dust</td>
<td>Nasal, lung</td>
</tr>
<tr>
<td>Nitrate/nitrite (cured/smoked foods)</td>
<td>Stomach</td>
</tr>
<tr>
<td>Salt</td>
<td>Stomach</td>
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<tr>
<td>Silica, crystalline (respiratory size)</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Carcinogen</td>
<td>Site</td>
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<tr>
<td>------------</td>
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</tr>
<tr>
<td>Skin, scrotal, lung, liver, esophageal, leukemia</td>
<td>Soots</td>
</tr>
<tr>
<td>Laryngeal, lung</td>
<td>Strong inorganic sulfuric acid mists (metal workers)</td>
</tr>
<tr>
<td>Endometrial, uterine</td>
<td>Tamoxifen (chemotherapy)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Thiotepa (chemotherapy)</td>
</tr>
<tr>
<td>Liver, all</td>
<td>Thorium dioxide (high temperature manufacturing)</td>
</tr>
<tr>
<td>Oral cavity/pharynx, larynx, esophagus, stomach, lung, kidney, pancreas, bladder</td>
<td>Tobacco smoke</td>
</tr>
<tr>
<td>Liver</td>
<td>Vinyl chloride (PVC manufacturing)</td>
</tr>
</tbody>
</table>

**Radiation Carcinogens**

<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many forms of cancer</td>
<td>Atomic bomb</td>
</tr>
<tr>
<td>Skin, bone</td>
<td>Radium</td>
</tr>
<tr>
<td>Lung, bronchus</td>
<td>Radon</td>
</tr>
<tr>
<td>Brain, nervous system</td>
<td>X-rays</td>
</tr>
<tr>
<td>Skin</td>
<td>Ultraviolet, B</td>
</tr>
</tbody>
</table>

**Biological Carcinogens**

<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many forms of cancer</td>
<td>Aging</td>
</tr>
<tr>
<td>Colon, rectal</td>
<td>Animal fat/low fiber</td>
</tr>
<tr>
<td>Liver</td>
<td>Contaminated cooking oil</td>
</tr>
<tr>
<td>Uterus, breast</td>
<td>Estrogen, steroidal</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatitis B and C</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma, Kaposi’s sarcoma</td>
<td>Human immunodeficiency</td>
</tr>
<tr>
<td>Cervical, anogenital, squamous cell carcinomas</td>
<td>Human papilloma</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma, adult T-cell leukemia</td>
<td>Human T-Lymphocytic, 1</td>
</tr>
<tr>
<td>Ovary</td>
<td>Ovulation</td>
</tr>
<tr>
<td>Bladder, liver, intestinal</td>
<td>Schistosomiasis (parasite)</td>
</tr>
<tr>
<td>Prostate</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Nasal</td>
<td>Wood dust</td>
</tr>
</tbody>
</table>

(Table adapted from Danaei et al. 2005; Chabner & Thompson 2013; Sloan & Gelband 2007)
TOBACCO SMOKE-RELATED CANCERS

Out of all of the human carcinogens listed on the previous page, tobacco smoke is responsible for the greatest number of cancer-related deaths in the United States. It is estimated that during the year 2008 cigarette smoking caused approximately 30% of all cancer deaths (American Cancer Society 2008). The 1-year survival rate for individuals diagnosed with lung cancer is approximately 41%; however, the 5-year survival rate for lung cancer (combining patients of all stages at time of diagnosis) drops to 15% (American Cancer Society 2008).

Because of the devastating consequences of tobacco smoking, patients need to be educated and offered support in their efforts to quit smoking.

HEREDITARY CANCER

In contrast to sporadic cancer, heritable forms of cancer do run in families. Only 5% to 10% of cancers are thought to be heritable (American Cancer Society, 2009). Heritable cancers are caused by germline mutations that alter genetic information in sperm or egg cells (gametes) involved in fertilization, thus passing a mutation on from one generation to the next.

Clinical Example: Theresa is a 21-year-old Ashkenazi Jewish woman. She is single and does not have children. Although she is currently cancer-free, Theresa worries about developing cancer. There is a significant family history of breast and ovarian cancer in Theresa's family. Because of the family history, Theresa’s mother underwent genetic testing for a hereditary breast and ovarian cancer syndrome last year. Her mother’s genetic test was positive for a mutation in the BRCA1 gene, a tumor suppressor. Women who have the mutation found in Theresa’s mother are at increased risk for breast and ovarian cancer.

BRCA1 is inherited in an autosomal dominant fashion, meaning that Theresa was born with a 50% chance to have the same BRCA1 mutation her mother has. The presence of the BRCA1 mutation does not guarantee that cancer will develop. For example, a woman born with a mutation in the BRCA1 gene has a 55% to 65% chance to develop breast cancer (Chen & Parmigiani 2007). She also has a 13% to 44% chance of not developing breast cancer. To learn more about her risks for cancer and preventive healthcare options, Theresa plans to visit a local cancer genetic counselor.
Elaine: Ovarian cancer dx age 46y, unilateral.
Claudia: Breast cancer dx age 46y, unilateral.
May: Breast cancer dx age 49y, unilateral. Breast cancer dx age 51y, contralateral breast, primary tumor.

**HERITABLE CANCER MODELS**

**Knudson's Hypothesis**
People who develop heritable forms of cancer are not actually born with cancer; instead, they are born with an increased risk to develop cancer. To explain why such individuals aren't born with cancer and may not ever develop cancer, Knudson put forth the "two hit" hypothesis in 1971 (Kerrigan, Kelly, & Hollen 2006).

When he published his now-famous hypothesis, Knudson was studying a specific tumor suppressor gene involved in hereditary retinoblastoma. His hypothesis stated that a single mutation in a tumor suppressor gene was insufficient to cause cancer. This is because every person has 2 copies of each tumor suppressor gene, one on each chromosome pair. Even if one copy of a tumor suppressor has a mutation in it, the second copy still functions normally, preventing cancer. However, if a second mutation occurs in the remaining functional copy of the gene, cancer develops.

Individuals who inherit a mutation in a tumor suppressor gene from a parent have that mutation in each cell of their body. Only one additional step is needed for cancer to develop. A second mutation in the other copy of that same tumor suppressor gene must occur, eliminating the function of both
copies of the gene. For individuals who develop sporadic cancer, 2 separate mutation events must happen during the person's lifetime. As a result, people who develop sporadic cancers tend to develop them at later ages than people who inherit a mutation from a parent.

Knudson's two-hit model explaining how the inactivation of tumor suppressor genes leads to cancer is illustrated below.

**Knudson's two-hit hypothesis for tumorigenesis**

a. Mutation in a normal cell, leading to sporadic cancer

b. Mutation in a cell with a germline mutation, leading to familial cancer

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**VOGELSTEIN'S MODEL**

In 1990, a second hypothesis describing the sequential development of gene changes leading to cancer was published (Fearon and Vogelstein, 1990). This second model is known as Vogelstein's model. Vogelstein developed the model while studying a hereditary form of colon cancer, familial adenomatous polyposis (FAP). Although Knudson's model described a sequence of events needed for cancer development, his model was limited to the involvement of a single gene. Vogelstein's model builds on the idea that a sequence of events is needed, expanding the theory to include multiple genes and numerous steps. Vogelstein created his model to explain the progression of lesions in the colon into polyps and eventually into cancer (see illustration below).

It is important to note that although both Knudson's hypothesis and Vogelstein's model were developed to explain disease progression in individuals with a heritable cancer syndrome, both models describe development of sporadic cancers as well. Each model also explains why people who develop sporadic cancers tend to develop them at later ages than people who inherit a mutation in a cancer-causing gene from a parent do.
Recognizing Heritable Cancers

Recognizing individuals at risk to have a heritable form of cancer allows physicians an opportunity for intervention, reducing the chance that such patients will develop cancer and/or increasing the survival rates for those who do. One of the best ways to detect persons at risk for heritable cancer(s) is to take a detailed, family history. Several guidelines for constructing a cancer family history, or pedigree, have been published (Bennett 2010; Schneider 1994). Pedigrees should include the following:

- Ethnicity
- Both maternal and paternal family members
- Detailed personal and family cancer history, including
  - type of cancer
  - location (unilateral versus bilateral)
  - age at diagnosis
  - current age or age at death
- Presence of any noncancer health findings or unusual physical features
- Description of any environmental carcinogenic exposures
- Any previous genetic test results
Once a pedigree has been obtained, it is important to confirm the history provided, when possible, by reviewing medical records (Johnson and Brensinger 2000). The information can then be evaluated to determine whether or not a particular patient has a history consistent with a heritable cancer.

Heritable cancers tend to

- Occur at younger ages than do sporadic cancers
- Affect both sides of the body
- Present as multiple types of cancer in the same person
- Manifest rare forms of cancer
- Affect multiple family members (in paired organs)
- Display an autosomal dominant pattern of inheritance

(Bennett 2010; Marsh and Zori 2002; Schneider 1994)

Although a family history is often a valuable tool for assessing risk to patients, it is important to note that people with heritable cancers do not always have a positive family history for cancer. There are multiple explanations for these negative family histories. One reason is that a certain percentage of individuals with hereditary cancers have them as a result of a new mutation (a mutation that occurred in the egg or sperm cell forming the individual but was not present in the somatic cells of the individual's parents). A second reason is that some hereditary cancers do not exhibit complete penetrance, meaning that family members may harbor a cancer susceptibility mutation but remain cancer-free. Another reason is that some families are small or have fewer people that are old enough to have developed a hereditary cancer(s).

CANCER SYNDROMES

Tumor Suppressor Genes
Very few hereditary cancer syndromes are known to be caused by oncogenes. In contrast, a great many cancer syndromes are caused by mutations in tumor suppressor genes.

Oncogenes
Hereditary cancers can be caused by mutations in any of the 3 types of genes discussed in this course: proto-oncogenes, tumor suppressors, or DNA repair genes. Because multiple cancers and other unusual physical findings are often present in individuals inheriting a mutation in one of these genes, the resulting disease is called a hereditary cancer syndrome.

DNA Repair Genes
DNA repair genes, sometimes called caretaker genes, cause cancer by allowing cells with mutations in additional genes to continue growing and dividing. As a result, many of the cancer syndromes caused by mutations in DNA repair genes have a significant clinical impact. Unlike many other cancer syndromes, those caused by DNA repair genes often greatly increase cancer risk in childhood.
Screening – General Population
Numerous professional organizations have published cancer screening guidelines for practicing physicians to follow. Many similarities exist among the recommendations; however, complete agreement between the professional organizations does not exist. The website for the American Academy of Family Physicians hosts a page summarizing screening guidelines from most major medical organizations.

For early detection of cancer in people without cancer symptoms, the American Cancer Society (ACS) recommends that people from ages 20 to 39 have a cancer-related checkup every 3 years. The ACS also recommends that people age 40 and older have a similar checkup annually. The checkup should include the procedures listed below, health counseling (smoking cessation, physical fitness plan, etc.), and examinations for cancers of the thyroid, testes, prostate, oral region, ovaries, skin, and lymph nodes. The guidelines outlined below may be found in their entirety at ACS.

**Breast**
- Monthly breast self-examination for women 20 and older
- Clinical breast examination every 3 years for women 20 to 39
- Annual clinical breast examination for women 40 and older
- Annual mammography for women 40 and older

**Cervical**
- Annual conventional Pap test or liquid-based Pap test every 3 years for women starting 3 years after becoming been sexually active, but no later than age 21
- Pap test may be performed every 2 to 3 years for women age 30 and older who have had at least 3 consecutive normal Pap tests
- Pap test may be discontinued in women who undergo a total hysterectomy and in women who are 70 years and older who have had 3 normal Pap tests in the last 10 years

**Colorectal**
- Annual fecal occult blood tests OR
- Flexible sigmoidoscopy every 5 years OR
- Combination of fecal occult blood tests and flexible sigmoidoscopy every 5 years OR
- Colonoscopy every 10 years OR
- Double-contrast barium enema every 5 years

Colorectal cancer screening is recommended for men and women 50 and older.

**Endometrial**
Women should be informed about the risks and symptoms of endometrial cancer and should be asked about any unexpected bleeding or spotting.

**Prostate**

- Annual Prostate-Specific Antigen (PSA) test for men age 50 and older
- Annual digital rectal examination (DRE) for men age 50 and older

Both PSA and DRE should be offered at age 45 to men who are at high risk (African-Americans or those with a strong family history).

### SCREENING – INCREASED RISK

**Prevention for Those at Increased Risk**

Included in the 2004 ACS guidelines are general recommendations for individuals who are currently cancer-free but who are at greater risk to develop cancer than people in the general population. Individuals who are at greater risk include those who have the following:

- A personal history of cancer
- A personal history of factors elevating risk (e.g., atypical hyperplasia of breast tissue, inflammatory bowel disease)
- Significant family history of cancer
- Family history of a hereditary cancer syndrome

People at increased cancer risk are often offered the same cancer screenings as the general population but at younger ages and/or at more frequent intervals (American Cancer Society 2004). For individuals at risk for a hereditary cancer syndrome, genetic testing may be offered in addition to these screening measures.

### CANDIDATES FOR GENETIC TESTING

Genetic testing for hereditary cancer syndromes is not appropriate for members of the general population. Guidelines for when to offer genetic testing to patients are available from the American Society of Clinical Oncology (ASCO).

ASCO recommends the following:

- Genetic testing for inherited cancer syndromes be offered with pre- and post-test counseling when all of the following criteria are met:
  1. personal or family history suggestive of an inherited cancer susceptibility
  2. available tests can be adequately interpreted
  3. test results will assist in diagnosis or impact management of the patient or at-risk family members
- Physicians discuss possible risks, benefits, and limitations of early detection and prevention options, which may have unknown or unclear efficacy in individuals at risk for an inherited cancer susceptibility syndrome.
• Healthcare providers make concerted efforts to protect the confidentiality of genetic information while communicating the importance of sharing risk information and test results with at-risk family members.

(ASCO 2010)

In addition, ASCO makes specific recommendations about genetic testing in children. ASCO recommends that genetic testing for cancer susceptibility in children be considered when there is sufficient chance of developing malignancy in childhood and/or evidence-based risk reduction strategies exist; in the absence of increased risk for childhood malignancy, genetic testing decisions should be delayed until the at-risk individual can make an informed decision (ASCO 2010).

GENETIC COUNSELING

Genetic Counseling for Hereditary Cancer Syndrome Testing
If a patient is determined to be an appropriate candidate for an available genetic test, genetic counseling should be included as part of the testing process.

<table>
<thead>
<tr>
<th>The genetic counseling process includes the following:</th>
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<tbody>
<tr>
<td>• Information gathering/initial risk assessment</td>
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<tr>
<td>• Discussion of identified risks/potential risks</td>
</tr>
<tr>
<td>• Education about available diagnostic/testing options</td>
</tr>
<tr>
<td>• Discussion of diagnosis/test results</td>
</tr>
<tr>
<td>• Education about healthcare options and available resources</td>
</tr>
<tr>
<td>• Follow-up counseling</td>
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</tbody>
</table>

(Johnson and Brensinger 2000; Plunkett and Simpson 2002)

During the course of genetic counseling, both verbal and written informed consent for the testing process are usually provided. Most institutions and laboratories require documentation of informed consent prior to testing a sample. However, informed consent is best thought of as a process rather than a piece of paper signed by the patient.

Not all patients offered testing will elect to proceed with it. The decision to pursue or decline testing is often correlated with the patient's perception of the potential risks and benefits of testing for both himself or herself and his or her family members. For an individual who already has cancer or findings suggestive of a cancer syndrome, the decision to pursue genetic testing may be relatively straightforward. However, for an individual who does not have any symptoms of a cancer syndrome but is at increased risk based on family history, a significant amount of time to weigh all options may be needed.

Should an individual proceed with testing, result disclosure is best done face to face, where post-test counseling can be provided immediately. A plan for the delivery of test results should be established prior to initiating testing. As with any life-altering medical information, a patient may have difficulty processing emotions related to genetic testing. For such patients, referral to a mental health specialist is helpful.
TEST YOUR KNOWLEDGE

If a genetic test is available and valuable healthcare information can be gained from it, it is considered standard of care to automatically order the test.

1. True
   - Feedback:
     Incorrect. When a clinically useful genetic test is available, patients should be informed about the test (including benefits, risks, and limitations) and be offered the opportunity to proceed with testing. Not all patients will elect to go through the testing process. Some reasons why a patient may decide not to be tested include expense, concerns over privacy, and psychological burden.

2. False
   - Feedback:
     Correct. When a clinically useful genetic test is available, patients should be informed about the test (including benefits, risks, and limitations) and be offered the opportunity to proceed with testing. Not all patients will elect to go through the testing process. Some reasons why a patient may decide not to be tested include expense, concerns over privacy, and psychological burden.

MANAGEMENT OF CANCER-FREE PATIENTS AFTER GENETIC TESTING

Disease-causing mutation detected
Patient management will reflect the syndrome for which the patient is at risk. Often management options include the following:

- Increased surveillance
  - physical exams
  - imaging studies
  - bloodwork/labs

- Lifestyle changes
  - exercise
  - reduced fat intake
  - reduction in radiation exposure
  - vitamins/antioxidants
  - stress reduction

- Prophylactic surgery
- Medication

No familial mutation detected
Patients who proceed through genetic testing and who are found not to have a previously identified familial mutation return to the population risk for cancer. These patients can be screened using the ACS guidelines for the general population.
Uninformative results
Much to the frustration of patients and healthcare providers, genetic testing does not always provide clinically useful results. For example, testing cannot accurately quantify cancer risk for cancer-free patients who are characterized by the following:

- Are the first persons in their families to pursue genetic testing and in whom no mutation is detected
- Receive results for which no clinical information has been gathered

These patients are best managed by implementing screening at earlier ages and by increasing screening frequency.

For patients who proceed with genetic testing and who are found to have a mutation associated with a cancer syndrome, special management recommendations are implemented. Often patients in this high-risk category are followed by cancer specialists and are managed with the goal of preventing development of cancer. Management guidelines also aim to increase the likelihood of early detection. Should cancer develop, management guidelines may in some cases beneficially affect progression.

TEST YOUR KNOWLEDGE

Depending on the test ordered, results may be reported as:

- Positive for a cancer-causing mutation
- Negative for the mutation(s) tested for
- Positive for mutation of unknown clinical significance

Choose one

1. True
   - Feedback:
     Correct. Although genetic testing can be a powerful and valuable tool, clinically useful results are not guaranteed.

2. False
   - Feedback:
     Incorrect. Depending on the condition tested for, the patient's medical and/or family history, and the type of technology the test utilizes, it is possible for a patient to either receive definitive results or uninformative results.

MANAGEMENT OF PATIENTS WITH CANCER

Patients with sporadic cancer
Patients with a sporadic form of cancer usually have several treatment options from which to choose. Treatment options will be influenced by the type of cancer, location, and the stage at which it is detected. Common treatment options include the following:

- Surgery
- Radiation therapy
Patients with hereditary cancer

Patients with heritable cancers are often provided treatment options similar to patients who do not have a cancer syndrome. In other cases, treatment options may be impacted by the syndrome.

**Clinical Example:** A child with ataxia telangiectasia (AT) who develops childhood cancer will likely be managed differently than a child without AT. Individuals with AT are especially sensitive to radiation and some chemotherapeutic agents. Children being treated for a malignancy will need lower exposures to many treatment options.

**SUMMARY**

- Three groups of genes are involved in the development of cancer:
  - **Oncogenes** function as proto-oncogenes to promote normal cell growth; a deleterious mutation in a proto-oncogene causes the gene to become an oncogene. Oncogenes cause cancer by becoming more active or gaining an additional function, resulting in more rapid cell growth.
  - **Tumor suppressor genes** normally function to regulate the timing of cell growth and division. A mutation in a tumor suppressor gene causes cancer by reducing the gene's normal activity or eliminating its function entirely, allowing for uncontrolled cell growth.
  - **DNA repair genes** are responsible for repairing genetic information; a mutation in a DNA repair gene may allow inaccurate genetic information to be passed onto daughter cells. Mutations in DNA repair genes lead to cancer by allowing mutations to accumulate in the genome (including mutations in proto-oncogenes and tumor suppressor genes), eventually leading to uncontrolled cell growth.

- For sporadic and heritable cancer to develop, a multistep sequence of events must take place. This sequence is best described by Vogelstein's hypothesis.

- One of the best ways to detect persons at risk for heritable cancer(s) is to take a detailed, 3-generation family history. It is important to remember that not all people with heritable cancers have a significant family history. Pedigrees should include the following:
  - ethnicity
  - maternal and paternal family members
  - detailed personal and family cancer history
  - presence of any noncancer health findings or unusual physical features
  - description of any environmental carcinogenic exposures
  - any previous genetic test results

- When comparing characteristics of sporadic cancers to heritable cancers, hereditary cancers more commonly
  - occur at younger ages
  - affect both sides of the body
  - cause multiple types of cancer in the same person
• cause rare forms of cancer
• affect multiple family members
• display an autosomal dominant pattern of inheritance

• Patients without cancer, but who are at increased risk for hereditary cancer(s), are usually managed with increased surveillance. Depending on the particular cancer syndrome, many patients are also offered prophylactic surgery, medications, and appropriate lifestyle changes as additional options.

• Patients with heritable forms of cancer are often offered treatment options similar to patients with sporadic cancers. Occasionally, however, individuals with heritable cancers do need to be treated differently.

• Many professional and patient resources are available online. Two popular professional websites include NCI and GeneTests. The NCI website also hosts extensive patient materials.

RESOURCES AVAILABLE THROUGH THIS MODULE:

• **AAFP Cancer Screening Guidelines**
  This document is a compilation of the cancer screening guidelines from most major medical organizations.

• **Addressing The Cancer Burden: At A Glance 2010**
  This overview page presents information on the prevalence of cancer in the US, breaking the incidence down by demographic category. Links to more comprehensive literature are included at the bottom of the page.

• **APC-Associated Polyposis Conditions**
  This article describes the clinical features of APC-associated polyposis conditions, which include familial adenomatous polyposis (FAP), attenuated FAP, Gardner syndrome, and Turcot syndrome.

• **Ataxia-Telangiectasia**
  This article describes the clinical features of ataxia-telangiectasia (A-T), including genetic testing, diagnosis, and management of the condition.

• **BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer**
  This article provides comprehensive information on the BRCA1 and BRCA2 and Hereditary Breast/Ovarian Cancer. It includes information on prevalence, screening, diagnosis, counseling and management, as well as extensive information on genetic testing and the genes themselves.

• **Chronic granulocytic leukemia (CGL)**
  This webpage provides a brief summary of Chronic granulocytic leukemia (CGL) and includes an image of cells affected by this form of cancer.

• **GeneTests**
  The GeneTests website offers an outstanding series of expert-authored GeneReviews that provide important information for clinicians to know about diagnosis, natural history, and genetic testing for genetic conditions. GeneTests.org also maintains databases of genetic testing laboratories and medical genetics clinics. There is no cost to use this website.
• **Hodgkin's lymphoma**
  This webpage provides basic information on Hodgkin's lymphoma as well as images of this cancer's effect on cells and a patient.

• **Informed Consent during Genetic Testing**
  Obtaining informed consent from patients is a vital part of the genetic testing protocol. Written documentation of informed consent is ideal. This page provides a list of what is generally included in informed consent.

• **Kaposi's sarcoma**
  Color image of Kaposi's sarcoma on the foot.

• **Kidney Cancer**
  This webpage provides comprehensive information on kidney cancer for both patients and health care professionals. It includes information on prevalence, prevention, screening, treatment, clinical trials, and relevant literature.

• **Melanoma**
  Image of a melanoma lesion

• **National Cancer Institute**
  National Cancer Institute provides various information. For the general public, patients, and health professionals, they offer consumer-oriented information on a wide range of topics as well as comprehensive descriptions of their research programs and clinical trials. Scientists will find detailed information on specific areas of research interest and funding opportunities. (From Their Website)

• **Pedigree Key**
  Key to symbols used in pedigree charts.

• **Pulmonary artery sarcoma**
  Black and white image of pulmonary artery sarcoma.

• **Report on Carcinogens (RoC)**
  This document provides information on substance that have the potential to cause cancer (carcinogens). A new version is released every two years.

• **The Cell Cycle & Mitosis Tutorial**
  This page explains each step of mitosis in detail and includes an illustration of each. There is also a video displaying mitosis.

• **The Skin Cancer Foundation**
  The Skin Cancer Foundation website provides comprehensive information for patients and health care professionals on all types of skin cancer.

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**REFERENCES USED IN THIS MODULE:**


PROFESSIONAL PRACTICE GAPS REFERENCES
