CHAPTER

1

Cancer Diagnosis and Treatment

Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type. That was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard?
—President Barack Obama (January 30, 2015; Precision Medicine Initiative)

A cancer genetic counseling session often begins with hearing the patient's cancer story: the symptoms that led to the suspicion of cancer, the way in which the diagnosis was made, and the subsequent treatment regimen. This chapter describes the process of making a cancer diagnosis, the systems used to classify tumors, and the current strategies for cancer treatment. The chapter will also briefly touch on the risk factors for cancer as context for a genetic counseling session.

1.1. The Diagnosis of Cancer

This section provides the information necessary to understanding a cancer diagnosis, from how cancer is diagnosed to the nomenclature used to describe the tumor and the treatment options that are available.

1.1.1. Cancer Detection

A diagnosis of cancer often begins with a worrisome symptom or problem on a medical intake or screening test. For example, a physical exam may reveal swollen lymph glands or unusual tenderness. A routine screening test, such as a colonoscopy, cervical Pap smear, or blood test,

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Katherine A. Schneider, Anu Chittenden, and Kristen Mahoney Shannon.

may identify the presence of atypical cells or an unusually high number of cells. A blood specimen that shows a dramatically high count of "blasts" (immature white blood cells) in a young child may point to the presence of acute lymphoblastic leukemia.

In many cases, patients have noticed warning signs of cancer (see Table 1.1). They may note a new physical finding, such as a breast lump, or they have health problems that are not abating over time (such as a persistent cough) or even getting worse (such as bleeding after a bowel movement).

People are more likely to experience symptoms or warning signs if their tumor:

- Is pressing on neighboring tissue and causes pain
- Is interfering with the functioning of normal tissue
- Has invaded the blood vessels to cause abnormal bleeding
- Has grown large enough to be palpated

A malignant tumor can be present for months, even years, before it is detected. The reasons why cancer detection can be so difficult are presented in the following sections.

1.1.1.1. Lack of Warning Signs

There may be no physical symptoms that signal the presence of early-stage cancer. Observable signs of cancer are more likely to be noticed as the cancer progresses. Sometimes, this means that the hallmarks of cancer, such as a lump, bleeding, or pain, indicate a malignancy that is already in an intermediate or advanced stage. However, most of the time, common symptoms are unrelated to cancer. If symptoms persist, they should be evaluated.

TABLE 1.1. General Signs and Symptoms of Cancer

- Fatigue or extreme tiredness that doesn't get better with rest
- Weight loss or gain of 10 pounds or more for no known reason
- Eating problems such as not feeling hungry, trouble swallowing, belly pain, or nausea and vomiting
- Swelling or lumps anywhere in the body
- Thickening or lump in the breast or other part of the body
- Pain, especially new or with no known reason, that doesn't go away or gets worse
- Skin changes such as a lump that bleeds or turns scaly, a new mole or a change in a mole, a sore that does not heal, or a yellowish color to the skin or eyes (jaundice)
- Cough or hoarseness that does not go away
- Unusual bleeding or bruising for no known reason
- Change in bowel habits, such as constipation or diarrhea, that doesn't go away or a change in how stools look
- Bladder changes such as pain when passing urine, blood in the urine, or needing to pass urine more or less often
- Fever or night sweats
- Headaches
- Vision or hearing problems
- Mouth changes such as sores, bleeding, pain, or numbness

Source: American Cancer Society (accessed 2021).

1.1.1.2. Imperfect or Lack of Screening Methods

To be effective, screening tests need to be easily performed, affordable, and accurate in detecting disease cases while limiting the number of false positive tests. The cancers must be detectable at earlier, more curable, stages and must occur at a frequency that justifies population screening. For example, a Pap smear is an effective screening test for cervical cancer, because it is a fairly common disease and early diagnosis has been shown to make a significant difference in survival. Cancers such as ovarian cancer have no known effective screening methods in detecting cancer reliably, although much work is being done in this area. Screening tests for less common forms of cancer are generally offered only to those known to be at high risk.

1.1.1.3. Elusive Premalignant Cells

Few organs can be readily and repeatedly sampled, which makes it difficult to monitor the organs for malignant or (even better) premalignant cells. At this point, only a few screening tests reliably detect premalignant cells, with colonoscopies being one of the best examples.

Cutting edge research is looking into the development of tests for very early markers of cancer through blood tests (see Chapter 8).

1.1.2. Making the Diagnosis of Cancer

The workup for cancer typically begins when other more likely explanations have been ruled out. For example, the differential diagnosis of frequent headaches includes vision problems, allergies, and stress. More serious possibilities, such as a brain tumor or neurological problem, are less likely to be entertained at the outset because of their relative rarity. Because of this, a common theme among members of families with hereditary cancer syndromes is that signs of cancer were initially ignored or downplayed by their providers.

The method by which the cancer will be identified depends on the tumor type (see Table 1.2). The presence of cancer may be suggested by physical exam, imaging studies, specialized blood

TABLE 1.2. How Cancer is Diagnosed

- Lab tests
  - Blood, urine, body fluid
- Imaging tests
  - CT scan
  - MRI
  - Nuclear scan
  - PET scan
  - Ultrasound
  - X-rays
- Biopsy
  - With a needle
  - With endoscopy
  - With surgery

Source: Adapted from National Cancer Institute, How Cancer Is Diagnosed.

TABLE 1.3. Some Common Tumor Markers Used in Diagnosis and Assessment of cancer

Tumor Marker	Type of Sample	Cancer
CA 19-9	Blood	Pancreatic, gallbladder, bile duct, and gastric cancers
CA-125	Blood	Ovarian cancers
Calcitonin	Blood	Medullary thyroid cancer
CEA	Blood	Colorectal and other cancers
Chromogranin A	Blood	Neuroendocrine tumor
Prostate-specific antigen (PSA)	Blood	Prostate cancer

Source: Adapted from National Cancer Institute, Tumor Markers in Common Use.

tests (see Table 1.3 for some common tumor markers detected in blood), or invasive procedures. Except in rare cases, biopsy is required to make a definitive diagnosis. For example, the diagnosis of pancreatic cancer may start with a symptom of weight loss and subsequent imaging, but it is the biopsy and subsequent pathologic analysis that will confirm the diagnosis.

Individuals will be referred to a medical oncologist either when the suspicion of cancer has been raised or following the initial diagnosis. As with most medical specialties, clinical oncology is divided into many subspecialties. Other members of the cancer care team include surgeons, radiologists, radiation oncologists, pathologists, and mental health professionals; the care of individuals with cancer requires a multidisciplinary team.

Cancer can be a high-burden disease on both patients and their families. Learning that one has cancer can engender feelings of shock, anger, intense sadness, and extreme anxiety. As patients enter cancer treatment, they may need to make major adjustments in their family responsibilities and workload. At many cancer centers, patients and their families have the opportunity to meet with a social worker or psychologist. Patient support groups may also be helpful.

1.1.3. Cancer Terminology

Hippocrates named the hard gray tumor tissue that extends into normal tissue "Carcinoma" for its crablike appearance. The Latin word for crab is *cancer*.

The terminology used to describe specific tumors can be daunting and it may be helpful to consider how these names are derived. Tumor nomenclature provides information about where in the body and in what type of tissue and cell the cancer originated. Cancer is currently still classified by the type of tissue and the primary site it originates in. However, with the advent of genomic analysis of tumors, classification systems may rely more heavily on mutational signatures.

1.1.3.1. Site of Origin

The medical term for a tumor is a *neoplasm*, which literally means new growth. Neoplasms can develop in almost every tissue of the body. The name of a neoplasm will usually first indicate the site in the body where the tumor has originated. As examples, a hepatocellular carcinoma is a liver cancer, and a rhabdomyosarcoma is a tumor of the striated muscle. Cancers of unknown primary are tumors that are metastatic at diagnosis and have unidentifiable sites of origin.

1.1.3.2. Tissue Type

The rationale underlying the name and classification of tumors can be found in embryology (see Table 1.4). In the early embryo there are three layers of germ cells: the ectoderm, the mesoderm, and the endoderm.

The type of tissue in which the neoplasm has occurred—as well as its embryological origin—will typically be indicated within the name of the tumor. There are several major categories of cancers: carcinoma, sarcoma, hematologic malignancies, mixed types, neuroectodermal.

- *Carcinomas*—Carcinomas occur in the epithelial cells covering the surface of the body and lining the internal organs. Carcinomas account for about 80–90% of all cancers. Carcinomas are divided into two major types: adenocarcinomas and squamous cell carcinomas. Adenocarcinomas arise mostly in organs with glands and occur in mucus membranes, and squamous cell carcinomas arise from cells lining body cavities. The most common sites of carcinomas are in the skin, lungs, female breast, prostate, colon and rectum, cervix, and uterus.
- *Sarcomas*—Sarcomas occur in tissues of mesodermal origin and are the rarest form of neoplasm. Sarcomas are solid tumors occurring in connective and supporting tissues, such as muscle, bone, or fat (see Table 1.5). Roughly, they can be classified into soft-tissue

TABLE 1.4. Derivation of Tissue Types

Embryonic Tissue	Tissue
Ectoderm	Some epithelial (skin, lining for most hollow organs), nerve tissue, salivary glands, and mucous glands
Endoderm	Some epithelial, including the lining of the digestive tract (except at open ends) as well as the epithelial lining of hollow structures formed as outpockets in the digestive tract
Mesoderm	Endothelium, bone and cartilage, muscle, fat, blood and lymph vessels, blood cells, also epithelial lining of uterus (endometrium), vaginal epithelium, and mucosa of the bladder

Source: Adapted from SEER Training Modules.

TABLE 1.5. Soft Tissue Sarcomas by Tissue Type

Name of Sarcoma	Related Normal Tissue Type
Angiosarcoma	Blood or lymph vessels
Desmoid tumor, also called deep fibromatosis	Fibroblasts, which are the most common type of cells in connective tissue
Ewing family of tumors	No obvious related normal tissue; may be a tumor of stem cells
Fibrosarcoma	Fibroblasts, which are the most common type of cells in connective tissue
Gastrointestinal stromal tumor (GIST)	Specialized neuromuscular cells of the digestive tract
Kaposi sarcoma	Blood vessels
Leiomyosarcoma	Smooth muscle
Liposarcoma	Fat tissue
Myxofibrosarcoma	Connective tissue
Malignant peripheral nerve sheath tumor (MPNST), also known as neurofibrosarcoma	Cells that wrap around nerve endings, similar to the way insulation wraps around a wire
Rhabdomyosarcoma	Skeletal muscle
Synovial sarcoma	No obvious related normal tissue; may be a tumor of stem cells
Undifferentiated pleomorphic sarcoma (UPS), previously called malignant fibrous histiocytoma (MFH)	No obvious related normal tissue; may be a tumor of stem cells or a distant relative of rhabdomyosarcoma

Source: Cancer.net (ASCO) (2020).

tumors and bone tumors (chondrogenic and osteogenic). There are other rare categories of sarcomas as well.

- *Leukemias, lymphomas, and myeloma*—Leukemia, lymphomas, and myeloma are cancers occurring in the lymph glands or bone marrow, which generates all of the cells of the circulatory system (see Figure 1.1 for an illustration of the complex blood cell lineage). Leukemias and lymphomas comprise about 10% of all cancers. Leukemias (which literally mean "white blood") and lymphomas are sometimes referred to as liquid tumors in order to differentiate them from carcinomas, sarcomas, and melanomas, which are collectively termed solid tumors. Myeloma is a disorder of plasma cells that are a normal part of the immune system. Myeloproliferative neoplasms constitute a category of conditions that vary in severity (see Table 1.6).
- *Mixed types*—The presence of more than one category of cancer can be reflected by the name such as carcinosarcoma.
- *Neuroectodermal tumors*—As the name implies, neuroectodermal tumors arise from ectodermal cells in the central and peripheral nervous system. Examples include gliomas, neuroblastomas, and schwannomas.

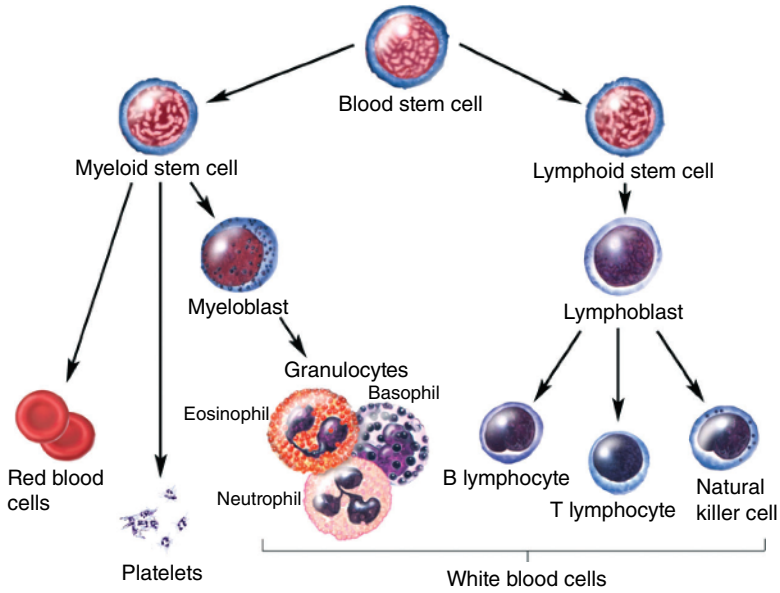

FIGURE 1.1. Blood cell development. *Source:* Terese Winslow.

TABLE 1.6. List of Some Myeloproliferative Neoplasms

Disorder	Cells Affected
Polycythemia vera	Red blood cells mainly, white blood cells, platelets
Essential thrombocythemia	Platelets
Primary myelofibrosis	Red blood cells, white blood cells, platelets

1.1.3.3. Cell Type

The name of a tumor will often describe the type of cell that has transformed into a cancer cell. Solid tumors can arise from adenomatous cells that are glandular or ductal, or from squamous cells that are flat. Tumors containing cells with features of both glandular and squamous cells may be called adeno-squamous carcinomas. Leukemias can arise from any of the various cells derived from myeloid or lymphoid lineages. Organs of the body are generally composed of more than one type of cell. Therefore, it is important to realize that more than one type of tumor can arise within the same organ.

1.1.3.4. Exceptions

Not all tumors are classified by these cell and tissue types. For example, cancers that resemble embryonic tissue are called blastomas; examples include neuroblastomas and retinoblastomas. Another exception are teratomas, which arise in tissues derived from all three germ cell layers.

To further complicate matters, some tumors have been named after the physicians who first described them. These include Ewing sarcoma, Hodgkin lymphoma, Kaposi sarcoma, and Wilms tumor.

1.1.4. Primary Cancer or Recurrence

Your patient explains that her mother was successfully treated for osteosarcoma at age 9 and was well until age 53 when she was diagnosed and treated for invasive breast cancer. Two years later she was found to have brain cancer and died at 56.

In deciphering a pattern of cancer in the family, it is important to determine whether a malignancy represents a primary cancer or a recurrence of the initial tumor. In this scenario, the mother's primary cancer is osteosarcoma, her breast cancer is a second primary, and the brain cancer may represent metastatic breast cancer.

1.1.4.1. Primary Cancer

A newly arisen tumor from a specific organ is considered a primary tumor. Individuals can develop more than one primary cancer, although this is uncommon. These second (or third) primaries may occur as a consequence of treating the initial cancer. As an example of this, women with Hodgkin lymphoma (previously called Hodgkin disease) who are treated with radiation to the chest have higher rates of breast cancer. Multiple primary cancers are also more likely in those with hereditary cancer syndromes.

1.1.4.2. Recurrence

A recurrence is the reappearance of cancer cells, either in the site of origin (local recurrence) or elsewhere in the body (systemic recurrence or distant metastasis). Recurrent cancer cells will demonstrate features that are consistent with the original tumor.

1.2. Tumor Classification

The tumor classification system helps dictate treatment regimens, predict prognosis, and provide a systematic approach that can be universally recognized and understood. Tumors are assessed for malignant properties or potential and, if malignant, are graded and staged. However, while benign tumors do not undergo the same classification process, properties of the tumor are still important.

1.2.1. Benign Tumors

The word "tumor" conjures up an image of cancer, yet not all tumors are cancerous. Thus, a lipoma (benign tumor of fat cells) may not be clinically significant, while a liposarcoma (malignant tumor of fat cells) represents a serious cancerous tumor. One of the initial steps in cancer

diagnosis is to send a tumor specimen to a pathologist, who will determine if the tumor has any malignant properties.

There are several differences between benign and malignant tumors. The most significant difference is that benign tumors do not spread to other sites of the body, whereas all malignant tumors have at least some metastatic potential. Benign tumors tend to be slow-growing. They are usually enclosed in a fibrous capsule and do not metastasize. Malignant tumors, in contrast, can proliferate rapidly and will, over time, spread to neighboring or distant tissues.

Despite the name, "benign" tumors are not always innocuous and can in fact cause significant risks of morbidity and mortality due to the following factors presented in the succeeding sections.

1.2.1.1. Location and Size

As a benign tumor grows, it may press against the normal surrounding tissue. This compression of the normal cell parenchyma can cause the normal cells to atrophy due to insufficient blood supply. In some sites of the body, there is sufficient space to tolerate a benign tumor. One example is the female uterus, in which fibroid tumors can grow to be quite large. In other sites, notably the brain and spine, there is little room for expansion and even moderately sized tumors can cause significant morbidity and mortality. Another example of a slow-growing tumor that can cause problems because of location is an abdominal desmoid tumor, which is a type of sarcoma. These types of tumors can lead to complications and even death due to sepsis, obstruction, ischemia, pulmonary embolism, and other factors. One part of diagnosis is determining the site of origin.

1.2.1.2. Excretion of Hormones

Benign tumors typically resemble their normal cell counterparts, which can be problematic if the cell type is hormone-secreting. The benign tumor, not constrained by normal cell regulatory systems, may begin to produce additional amounts of hormones. Although benign tumors are generally less efficient at hormone production than normal cells, the sheer volume of tumor cells can result in massive—and toxic—levels of hormone being produced. For example, most pheochromocytomas are benign tumors of the adrenal gland that produce the hormone epinephrine, which triggers the "fight or flight" response. Excess levels of epinephrine caused by the pheochromocytoma can result in alarmingly high blood pressure and, if untreated, can increase the risk of stroke or myocardial infarction.

In some cases, a benign tumor can be considered a precancerous tumor, that is, a tumor with malignant potential. Cells proceed through multiple steps before reaching a malignant state and some benign tumors may actually be malignant precursors. This has been shown to be the case for several types of cancer, such as certain pigmented moles (nevi) that can evolve into malignant melanoma, and adenomas of the colon, which can eventually transform into adenocarcinomas.

Note that benign tumors typically end in the suffix *-oma*, which means "a tumor of" without the preceding "carcin" or "sarc." Examples are meningioma and glioma (two types of brain tumors). There are exceptions to this nomenclature, notably melanoma, which is a highly malignant skin cancer. *In situ* tumors are early-stage malignant tumors. The following sections address the classification of malignant tumors.

1.2.2. Tumor Grading

Tumor grading involves analyzing the histological appearances and biological properties of the tumor in order to determine the extent to which the tumor resembles normal tissue. Histology is the study of the structure and composition of cells, tissues, and organs. A tumor that shows only subtle differences from normal tissue will be considered low grade (well-differentiated), while a tumor that bears little or no resemblance to its normal counterpart is of high grade (poorly differentiated). (See Table 1.7.)

Tumor grading is also based on the degree of cell differentiation that is present. Cell differentiation is the process by which newly formed (immature) cells evolve into different kinds of mature cells. Tumors are graded on whether their cells appear well differentiated, moderately differentiated, or poorly differentiated. (See example in Figure 1.2.)

TABLE 1.7. Histological Grades of Tumors

GX Grade cannot be assessed
G1 Well differentiated (low grade)
G2 Moderately differentiated (intermediate grade)
G3 Poorly differentiated (high grade)
G4 Undifferentiated (high grade)

Source: National Cancer Institute, FactSheet: Tumor Grade. Public domain.

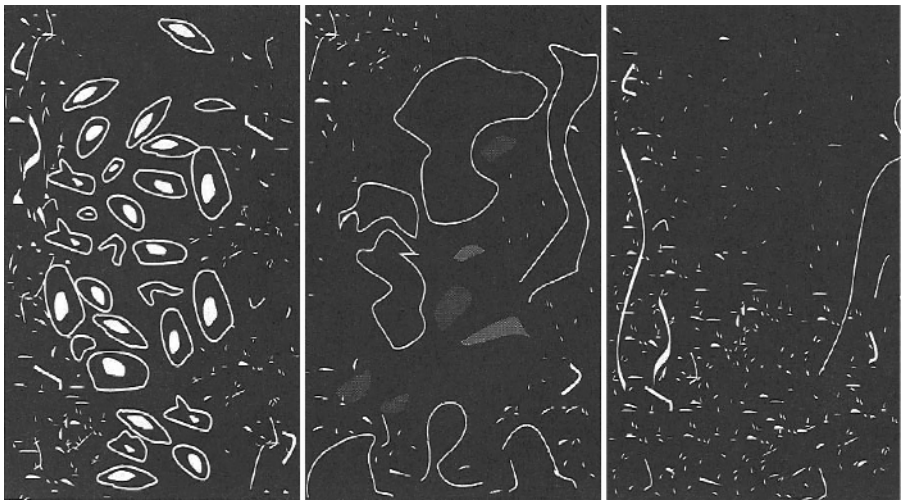

FIGURE 1.2. Cellular differentiation. The differences between a well-differentiated tumor cell (left), a moderately differentiated cell (middle), and a poorly differentiated cell (right) are shown. Adapted from Pfeifer and Wick (1991), John Wiley & Sons.

Tumors containing a few atypical cells are considered to be dysplastic, which is a premalignant state. Low-grade (well-differentiated) tumors tend to be slow-growing and less aggressive, while higher-grade (moderately or poorly differentiated) tumors tend to be fast-growing and more aggressive with a greater potential to metastasize. Tumors with a complete loss of normal differentiation are described as being anaplastic.

It is important to realize that the specific criteria used to grade a tumor are far from exact. Accurately grading a tumor depends on the pathologist's skills and expertise. In cases of rare and/or unusual tumors, it may be useful to have the tumor slides reviewed by a second pathologist.

1.2.3. Staging

The natural course of a malignancy is to grow and spread to other organs of the body. The purpose of staging is to determine the extent of disease progression in a specific patient, to estimate prognosis, and help determine the best treatment plan. Staging also provides a common set of criteria for oncologists and other medical specialists and provides a system for grouping patients in research treatment trials. Staging includes pathology examination of the tissue, biopsy of the lymph nodes, tumor markers, and imaging of surrounding areas for sites of possible metastases.

Staging can occur at different time points during the course of diagnosis and treatment. Initial staging, also called clinical staging, occurs on the basis of the workup of the cancer, prior to any definitive treatment. Pathological staging occurs after surgical resection and analysis of the tumor and regional lymph nodes. Post-therapy or post-neoadjuvant therapy staging occurs after the cancer has been treated (radiation, chemotherapy, or hormone therapy). Restaging occurs if there is recurrence of the cancer.

The clinical staging system most commonly used worldwide is the TNM system. The TNM system was developed by the American Joint Committee on Cancer Staging (AJCCS) and the International Union Against Cancer (IUAC) in an effort to standardize the staging criterion. The premise of staging is that cancers of the same site and histology will follow similar patterns of disease progression and will respond similarly to the same treatment regimens. Staging occurs after the initial assessment of the tumor and serves as a snapshot of the tumor prior to treatment. As treatment progresses, the tumor may be restaged as necessary. The current form of the IUAC is the Union for International Cancer Control (UICC).

The TNM system classifies cancer into Stages 0–IV, with Stage IV disease being the most advanced. Staging is made by assessing the size of the primary lesion, degree of invasion, and presence or absence of lymph node involvement or distant metastases. The more advanced the cancer, the higher each variable is graded. The three variables are specifically defined as:

- T—The extent of the primary tumor. This category considers the overall size and appearance of the tumor. Tumors are classified as being Tis (*in situ*), T1, T2, T3, or T4. *In situ* tumors are those that are confined to the cells lining the organ. Carcinomas and melanomas are the only cancers with an *in situ* stage. T4 tumors have invaded into tissues around the organ of origin.

- N—The extent of lymph node involvement. This is a strong predictor of systemic involvement. The lymph nodes are the gateway to the lymphatic or circulatory systems. Nodes can be classified as N0, N1, N2, or N3.
- M—The extent of distant metastases. Distant metastases are either absent (M0) or present (M1). The presence of distant metastases indicates an advanced stage of cancer.
- The specific criteria used to define each variable in the TNM system depend upon the organ involved. Table 1.8 describes the TNM system for medullary thyroid carcinoma. Note that a particular stage of cancer can be composed of different TNM combinations.

Staging is an integral part of diagnosis and is performed for every tumor type. Because malignancies vary greatly across different organs and tissues, not all cancers are staged using the TNM system alone (https://training.seer.cancer.gov/staging/systems/schemes/). In these cases, other classification systems have been developed. Examples include:

- FIGO staging of gynecological tumors
- Gleason scores for prostate cancers
- Ann Arbor classification of lymphoma

1.2.4. Genetic Analysis of the Tumor

Cancer is a disease of uncontrolled cell growth caused by genetic changes. Tumor histology is sometimes supplemented with different types of genetic analysis to further characterize the tumor and perhaps suggest additional therapies. These have become increasingly sophisticated over time.

TABLE 1.8. TNM Cancer Staging of Medullary Thyroid Carcinoma

Stage I	T1 N0 M0
Stage II	T2 N0 M0 or T3 N0 M0
Stage III	T1 N1a M0 or T2 N1a M0 or T3 N1a M0
Stage IVA	T4a N0 M0 or T4a N1a M0 or T1 N1b M0 or T2 N1b M0 or T3 N1b M0 or T4a N1b M0
Stage IVB	T4b Any N M0
Stage IVC	Any T Any N M1

T (Primary tumor): T1 = Tumor ≤2 cm; T2 = Tumor >1 cm but not >2 cm; T3 = Tumor >4 cm limited to thyroid or any tumor with minimal extrathyroid extension; T4a = tumor of any size extending beyond thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve; T4b = tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels. N (Regional lymph nodes): N0 = no regional lymph node metastasis; N1 = Regional lymph node metastasis; N1a = Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes); N1b = Metastasis to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII). M (Distant metastases): M0 = No distant metastases; M1 = Distant metastases.

Source: American Joint Committee on Cancer (2010), pp. 114–115. Springer Nature.

1.2.4.1. Molecular Studies

Molecular studies provide a closer analysis of tumor cells that further classify these cells into molecular subtypes. This allows more individualized treatment options and better prognostic predictions. (See Figure 1.3.) Here are examples of molecular studies that are important in this process:

- Whole-exome or whole-genome DNA sequencing
- Microsatellite instability
- DNA copy number variation
- DNA methylation
- Genome wide mRNA levels
- MicroRNA levels
- Protein levels

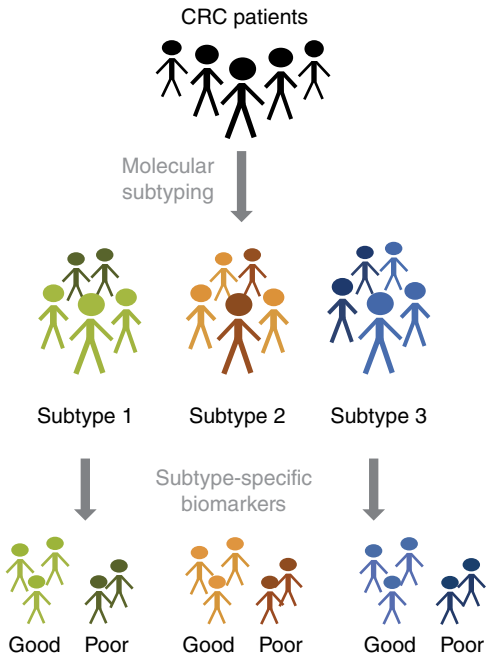

FIGURE 1.3. Molecular subtypes of colorectal cancer: Improved prognostication of CRC by molecular-subtype-specific biomarkers. Schematic illustration of the principle of CRC patient prognostication by combining molecular subtyping with subtype-specific prognostic biomarkers. Molecular subtyping is employed to reduce the major inter-tumor molecular diversity of CRC and allows patient prognosis to be more accurately predicted within each subtype by application of subtype-specific prognostic biomarker panels. Patients with good or poor prognosis are indicated. *Source:* Bramsen et al. (2017). With permission of Elsevier.

Genomic analysis has yielded a tremendous amount of information about shared genetic variation in cancer cells. Testing of tumors (somatic analysis) yields the sum of mutations from the fertilized egg to the time of tumor development. The result has been the classification of cancers through somatic "mutational signatures" (common within and among different cancer types). There are currently 30 mutational signatures that have been characterized (https://cancer.sanger.ac.uk/signatures/signatures_v2/).

Prior to genomic analysis, one of the clearest examples of a somatic signature was in DNA mismatch repair. Microsatellite instability, a marker for defective DNA mismatch repair, had been used to screen patients who may have Lynch syndrome. Currently, mutational signatures are helpful in determining likelihood of response to specific treatments. One example of this is with *BRCA1* and *BRCA2*. Tumors with homologous recombination deficiency (HRD), typical of *BRCA*-mutated tumors, identified by common mutational signatures are more likely to respond to a specific type of treatment, PARP inhibitors, than those with low HRD scores.

1.2.4.2. Malignant Cells Play Tricks

There are special properties of malignant cells that differentiate them from normal cells. Knowledge of how cancer cells differ from normal cells can be helpful for diagnosis, staging, and treatment.

On a cellular level, malignant cells share specific common abilities. They can:

- Initiate signal transduction pathways leading to mitosis (giving cells the ability to grow and divide outside of the normal signaling pathways).
- Resist normal signals that inhibit growth or cause programmed cell death (apoptosis).
- Acquire genetic instability, which can be divided into two major types:
  1. Chromosomal level (e.g., gains, losses, translocations, duplications, deletions, etc.)
  2. Nucleotide level (e.g., mutations in DNA repair genes)
- Induce angiogenesis (the growth and proliferation of blood vessels towards them). This allows them to obtain nutrients and energy and shed waste.
- Invade nearby normal tissue and spread to other areas through the circulatory system.
- Hide from the immune system (adaptive immune resistance) by:
  - Presenting antigens (substances on the outside of a cell that can elicit an immune response) that make them look more like normal cells
  - Removing or reducing antigens that would identify them as abnormal
  - Producing substances that suppress the body's immune response
  - Producing an environment of chronic inflammation (which promotes tumor growth) rather than acute inflammation (which suppresses tumor growth)

1.3. Cancer Treatment

With a diagnosis of cancer, patients and their families are thrust into a world with its own vocabulary and complicated treatment decisions. There are two overall aims of cancer treatment: to prolong life with curative intent and to relieve suffering with palliative care.

A tumor is composed of a patchwork of cell populations. It is important to recognize that clinical cure from cancer is defined as the absence of any detectable evidence of disease rather than the elimination of every single cancer cell. Oncologists hope to reduce the number of cancer cells to a negligible amount that will not cause any significant symptoms or problems over the person's remaining life span. The treatment of cancer is a delicate balancing act to eradicate the tumor while limiting the amount of harm to the patient.

The treatment of cancer is divided into local therapies and systemic therapies. Local therapies include surgery, radiation, cryotherapy, and laser therapy. Systemic therapies include chemotherapy, hormonal therapy, and biologic agents. The succeeding sections present information on the major types of cancer treatments.

1.3.1. Surgery

Surgical resection (removal) is the most effective strategy for treating localized disease and is the preferred strategy for eradicating solid tumors. The aim of surgery is to remove the entire tumor, which generally also requires removing a margin of surrounding healthy tissue. Surgical resection is most successful if the tumor is slow-growing, confined to a single organ, and can be removed without compromising any vital organs. Surgical risks include the small possibility of death related to the procedure or anesthesia, infection, short- or long-term disabilities, and disfigurement. The possible adverse effects of surgery are influenced by many factors, including the location of the tumor, extent of the surgery, and general health and age of the patient. Patients may be given radiation treatments and/or chemotherapy either prior to surgery (neoadjuvant therapy) or following surgery (adjuvant therapy).

There are seven major types of surgery used in oncology, presented in the succeeding sections (adapted from ASCO cancer.net and American Cancer Society).

1.3.1.1. Diagnostic

The main purpose of the surgical procedure is to confirm the diagnosis of cancer. This is typically done through a biopsy or aspiration of the cells. The type of procedure may depend on the organ and the accessibility of the area of concern.

1.3.1.2. Staging

Staging surgery involves assessing the extent of the tumor and may involve removing all or part of the tumor, removing lymph nodes around the tumor, and examining the area for spread of the cancer.

1.3.1.3. Curative/Tumor Removal

Curative surgery may be done when the tumor is localized to one organ and has not spread. This involves trying to remove the tumor completely. Chemotherapy and radiation may be given before or after surgery if needed.

1.3.1.4. Debulking

Debulking involves removing as much of the tumor as is possible without causing harm. If a tumor is large or has spread locally, it may not be possible to remove all of the tumor without causing damage to surrounding tissue. Because the tumor cannot be removed completely, additional treatment is often required before or after surgery.

1.3.1.5. Palliative

The purpose of palliative surgery is to reduce pain or symptoms caused by advanced disease rather than trying to eradicate the cancer. For example, a spinal cord tumor can cause difficulty walking and severe pain; surgery may alleviate symptoms. In most cases, the relief of pain or other symptoms from palliative surgery is only temporary.

1.3.1.6. Risk-reducing

Risk-reducing surgeries are often done in the high-risk setting to reduce or eliminate the risk for certain cancers. For instance, women who have a *BRCA1* pathogenic variant may elect to have bilateral salpingo-oophorectomies to reduce the risk for ovarian cancer.

1.3.1.7. Reconstructive

Reconstructive surgery can be done to help restore the appearance or function of an organ after therapy. Women having a mastectomy for breast cancer may choose to have reconstructive surgery at the same time as or after surgery for treatment.

Additional surgical procedures include the placement of a port catheter or pump to administer chemotherapy more easily.

1.3.2. Radiation Therapy

The aim of radiation therapy is to destroy tumor cells within the field being radiated. Radiation therapy can be used prior to or instead of surgery to shrink tumors or after surgery to destroy remaining local cancer cells. Radiation can also be used to shrink inoperable tumors or for palliative care to relieve symptoms.

Radiation therapy involves targeting selected doses of ionizing radiation to the tumor site. The field of radiation can be compared to the beam of a flashlight. The radiation beam will be strongest at the center of the targeted site, but the "scatter" beam can also inflict damage to cells. This may be a benefit of radiation therapy because it can destroy cancer cells that have begun to spread locally but can also lead to side effects. Tumor cells outside the field of radiation will not be affected, so radiation therapy is not an effective strategy for cancers that have metastasized.

How does radiation therapy work? The ionizing radiation deposits packets of energy into the cell, which (1) directly damages DNA and (2) generates reactive oxygen species that also damage DNA and results in programmed cell death (apoptosis) and/or blocked proliferation. Cells will either die immediately upon exposure or when they later attempt to undergo mitosis.

Cancer cells that are actively dividing at the time of the radiation exposure are most vulnerable to radiation; higher doses of radiation are needed to destroy quiescent cells (ones that are not actively dividing) and slow-growing tumors with infrequent cell divisions. In addition, radiation kills cells by generating reactive oxygen species. Thus, oxygen-poor tumors have some protection against radiation and require higher doses of radiation.

Radiation doses used to be measured in rads but are currently measured in units of Gray (Gy); a centiGray (cGy) is equivalent to a rad. Radiation therapy varies based on intent and cancer type. The dosages and total radiation exposure will differ depending on the tumor's location and size and the patient's tolerance of the treatments.

The effectiveness of radiation therapy depends largely on the tumor type and the sensitivity to radiation. One large dose of radiation may be more effective than multiple small doses, which give cancer cells a chance to regrow, but it is also more toxic to normal tissue. Typically, only a proportion of cancer cells are destroyed by a single dose of radiation.

Unfortunately, a proportion of normal cells within the field of radiation are also destroyed by the exposure to radiation. This is the major downside of radiation therapy, and the toxicity must be monitored throughout the course of treatment. To determine the optimal radiation dose, radiation oncologists will consider the radiation sensitivity of the tumor, the bulk of disease, and the maximum amount of radiation that will be tolerated by the normal tissue. Normal cells generally recover faster than their malignant counterparts. Since normal stem cells infrequently divide, they are generally less vulnerable to radiation damage.

1.3.2.1. Types of Radiation Therapy

There are two main types of radiation therapy: external beam radiation therapy and internal radiation therapy. Most types of therapy involve external therapy where a patient is in a machine that directs radiation towards the tumor. By contrast, internal therapy involves putting a source of radiation directly inside the body.

External beam therapy involves the use of three different particles: photons, protons, and electrons. Photon particles are used commonly for most standard radiation treatments. This type of therapy can damage normal tissue adjacent to the tumor because photons scatter radiation as they are traveling through the body. Proton beam therapy (using high-energy positively charged protons) does not scatter in the same manner and will stop within the tumor, so this type of therapy is typically used when tumors are close to very important areas of the body, such as the brain. Because of the precise targeting of the tumor, there may be fewer side effects with this type of radiation. However, it requires the use of very expensive large machinery and special expertise of the operator. Electron therapy uses negatively charged electrons that are limited in the area that they can reach, so the use of this therapy is limited to skin or tumors under the surface of the skin.

Types of external beam radiation therapy (EBRT) include 3-D conformal, intensity-modulated, image-guided, tomotherapy, stereotactic radiosurgery, or stereotactic body. All of these use imaging to try to map the precise location of the tumor, either prior to administration and/or during the course of treatment. For most forms of EBRT, patients undergo treatment once a day, 5 days a week, for 3–9 weeks. People who undergo external beam radiation are generally not "radioactive" after treatment.

Internal radiation therapy can be divided up into two types: solid source (brachytherapy) and liquid source (systemic therapy). Brachytherapy can be given through three different methods which include interstitial (placed directly within the tumor itself), intracavity (placed within a body cavity), and episcleral (used specifically for certain tumors of the eye). Radiation can also be given systemically through intravenous or oral administration, although this is less common.

Brachytherapy is typically given as low-dose or high-dose. The most common example of brachytherapy is the use of radiation seeds for early-stage prostate cancer. This involves implanting dozens of seeds directly into the prostate. Radiation is given off at a low dose, and the seeds may be removed after 1–7 days or may remain implanted for life. High-dose implants can provide a greater level of control of the dose but requires multiple treatments and, therefore, hospitalizations over time. The time for high-dose implants is usually 10–20 minutes per treatment for 2–5 days or once a week for 2–5 weeks. Another example of brachytherapy is called selective internal radiation therapy (SIRT) or radioembolization, where tiny beads of radioactive material are put into a blood vessel that feeds the liver. These beads are trapped in the smaller blood vessels that surround the tumor and will hopefully destroy the cancer cells. The procedure requires careful mapping of the arteries around the liver, with a planning angiogram done 1 to 2 weeks prior. While the procedure itself only takes about an hour, patients may have to lay flat for a number of hours to ensure that any bleeding has stopped, since a catheter is inserted into an artery in the groin for delivery of the beads.

An example of oral systemic therapy is I-131 radioiodine therapy used for the most common types of thyroid cancers (papillary and follicular), which is typically given by mouth through a capsule. In order to ensure that the radioactive iodine is most effective, patients must have high levels of thyroid-stimulating hormone (TSH), which helps direct the iodine to the thyroid gland. The treatment is given through iodine because its only use for our bodies is to make thyroid hormones. A patient swallows the dose of radioactive iodine, which is absorbed quickly and helps kill tumor cells safely and effectively. For this internal therapy, patients may be asked to avoid contact with other people for a short period of time, since they can excrete or give off radiation.

The side effects of radiation depend on the anatomic site being radiated. These side effects include hair loss if the radiation is to the head, or diarrhea and cystitis if it is to the pelvic area. Radiation may also cause fatigue, redness of the skin, or scarring of the tissues. Long-term effects can include cataracts (irradiated eyes) and sterility (irradiated sex glands). The lungs, liver, kidneys, and heart are also sensitive to radiation damage. These late responses can manifest months or years after the conclusion of treatment.

Radiation therapy in children can cause damage to bone and soft tissues, leading to reduced growth or deformity. Radiation therapy can also cause a second cancer, most commonly leukemia, or lymphoma, or, if in the field of radiation, breast cancer, thyroid cancer, or sarcomas.

1.3.3. Chemotherapy

The first clinical use of chemotherapy was in 1942, when highly toxic nitrogen mustard was used to treat lymphoma. Chemotherapy is systemic therapy that has the capability of destroying cancer cells throughout the body. Most drugs are given intravenously, but some are administered orally, even in pill form. The aims of chemotherapy are to further increase the chance that the

tumor is eradicated, to prevent or delay metastases, or to palliate symptoms. Current chemotherapy is mainly conducted in an outpatient setting.

Chemotherapy can effectively destroy actively dividing cells but is much less effective against quiescent (nondividing) cells. A course of chemotherapy can consist of a single drug, but often involves a combination of drugs with different mechanisms of action. The efficacy of a particular drug depends on the inherent tumor sensitivity and its absorption, metabolism, distribution through the tumor, and excretion out of the body. If chemotherapy is being given for advanced stage cancer, then the regimen of drugs may need to be altered during the course of treatment, because the remaining tumor cells may have become resistant to the agents that have previously been used.

The properties of the tumor will determine the chemotherapeutic regimen. Chemotherapy can also be given for pain relief or to stabilize bodily functions. The total number of chemotherapy courses administered will depend on the goal of therapy as well as the drug's effectiveness and toxicity. Typically, each course is spaced out in 1- to 3-week intervals in order to give the normal cell population a chance to recover.

Common side effects of chemotherapy include the loss of all body hair and the erosion of the mucosa of the gastrointestinal tract, leading to mouth sores, ulcers, and other digestive problems. Most types of chemotherapy cause bone marrow toxicity, leading to a decrease in white cells, platelets, or red cells. A drop in white blood cells temporarily increases the risk of infection. Chemotherapy drugs can also cause permanent damage to nonrenewing tissues, including the heart and nervous system, and can cause sterility and, in women, temporary or permanent premature menopause.

Classes of chemotherapy drugs include alkylating agents, antimetabolites, plant alkaloids, topoisomerase inhibitors, antitumor antibiotics, mitotic inhibitors, and others.

Chemotherapy is still an integral part of current cancer therapies for many tumor types. However, much of the focus in drug development is on more targeted therapies based on the molecular characteristics of cancer.

Examples of combination chemotherapy drugs for common cancers

Breast cancer	AC (doxorubicin, cyclosphosphamide)
Colon cancer	FOLFOX (5-fluorouracil, leucovorin, oxaliplatin)
Pancreatic cancer	Gem/Abraxane (Gemcitabine/albumin-bound paclitaxel)

1.3.4. Targeted Therapy

Targeted therapies are treatments that target specific molecules or pathways to block the growth, progression, and spread of cancers (National Cancer Institute, Targeted therapies). Targeted therapies differ from traditional chemotherapies in that they are chosen based on the properties of the cancer cells themselves rather than killing all rapidly dividing cells. Some of these types of therapies are cytostatic (inhibiting cell growth and division) rather than cytotoxic.

Targeted therapies include:

- Hormonal agents
- Signal transduction inhibitors (including PARP inhibitors)

- Immunotherapy
- Angiogenesis inhibitors
- Antibody drug conjugates

1.3.4.1. Hormonal Agents

Hormonal agents have been used for many years to treat or prevent recurrence of cancers. Steroid and nonsteroid hormones are actively involved in cellular proliferation and differentiation. Many tumors are hormone-driven, including cancers of the prostate and breast. These types of tumors have hormone receptors that can be targeted by hormonal therapy. Hormone (or trophic) therapy aims to shrink tumors by reducing the amount of available hormone and/or by inhibiting the binding of the hormone to the receptor. These agents can be used to treat advanced cancer or can increase the likelihood of cure if given after surgery or other treatment. Tamoxifen is an example of an antihormonal agent that successfully reduces breast cancer recurrence by targeting estrogen receptors. One advantage to hormonal agents is that they are generally less toxic than conventional chemotherapy.

1.3.4.2. Signal Transduction Inhibitors (including PARP inhibitors)

There are many different examples of signal transduction inhibitors in clinical use, including EGFR-related tyrosine kinase inhibitors, such as erlotinib for the treatment of lung cancer. Genetic counselors will most often see the use of PARP (poly ADP-ribose polymerase or PARPi) inhibitors for treatment of *BRCA*-related breast or ovarian cancer. PARP inhibitors block single-strand DNA damage repair in cells with non-functioning *BRCA1* or *BRCA2* (and possibly other DNA damage repair genes) harboring homologous repair deficiency (HRD). Tumor cells require this repair system in order to avoid programmed cell death (apoptosis) as illustrated in Figure 1.4.

Tumor cells can regain DNA repair deficiency through reversion mutation that restores the tumor cells' ability to undergo homologous repair (HR) and upregulating other DNA repair pathways. Resistance to PARP inhibitors can also occur with mutations in the PARP gene itself that prevent interaction with the inhibitor. The use of combination therapies (PARPi plus immunotherapy) may be more effective in treating cancers by targeting more than one pathway.

Side effects of PARPis can include an increased risk for infection, bleeding, fatigue, shortness of breath, diarrhea, changes in digestion and taste, headache, and others.

1.3.4.3. Immunotherapy

The immune system may not always recognize a tumor as a threat because its cells are native to the body rather than seen as a foreign substance. Immunotherapy seeks to re-engage the body's immune system to recognize and fight tumors. It has become a major focus of experimental treatments because of its possible use in many different types of cancers.

Types of cancer immunotherapy include:

- Immune checkpoint blockade therapy
- Adoptive cell transfer (in particular, CAR-T)

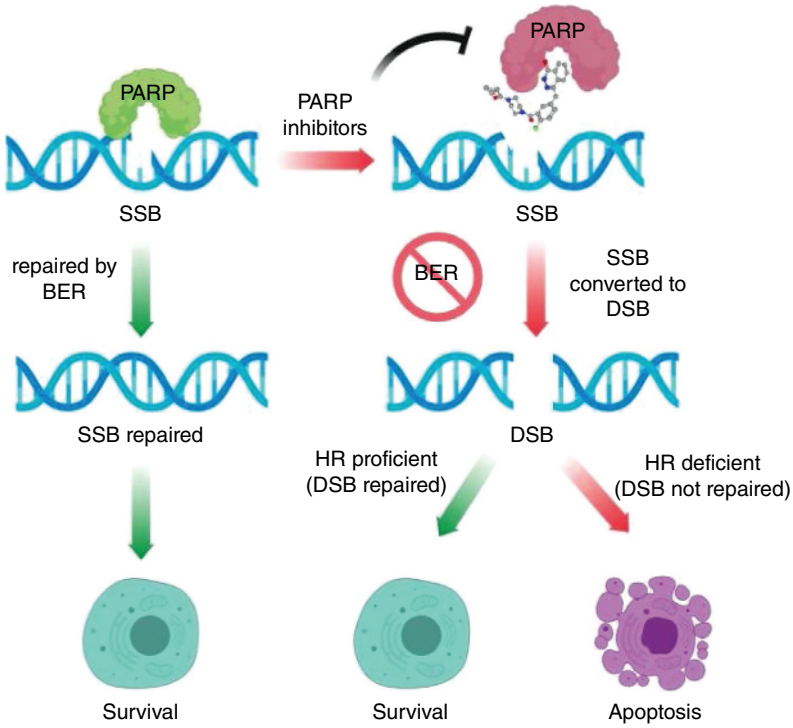

FIGURE 1.4. There are several mechanisms by which the tumor cells can reverse their "BRCA-ness," one of which is through reversion mutation that restores the tumor cells' ability to undergo homologous repair (HR). *Source:* Zheng et al. (2020). With permission by Elsevier. Licensed under CC BY 4.0.

- Bispecific antibody T-cell engagers
- Oncolytic virus therapy
- Vaccines
  - Therapeutic
  - Cancer preventive—Lynch syndrome
- Gene therapy

1.3.4.3.1. Immune Checkpoint Blockade

Immune checkpoint blockade (ICB) therapy is a therapeutic approach to release the brakes on the immune system and promote anti-tumor immunity. Tumor cells often express inhibitory receptors that block binding by other molecules that would otherwise escalate the immune response by stimulating the growth of T-cells and increasing the production of cytokines and other factors.

Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4/CTLA4)

CTLA-4 was the first target of immune checkpoint blockade therapy successfully developed as a treatment for cancer patients. It is an inhibitory receptor that downregulates the initial T-cell activation response by competing with CD28 for B7 ligands. It also inhibits proliferation of T-cells and decreases IL-2 secretion. It is currently used clinically in melanoma and in combination therapy for other solid tumors.

Programmed Death 1 (PD-1/PD1 or PD-L1/PDL1)

PD-1 has a similar inhibitory effect on the immune response by binding PD-L1 (ligand to this receptor). PD-1/PD-L1 antibodies have shown broad clinical benefit across solid tumors and are currently used for treating multiple cancers, including any tumor with microsatellite instability.

Limitations of ICBs include that they can cause severe immune-related adverse events, responses can take months to develop, and they may only be effective in a small percentage of tumors with specific characteristics.

Current examples of ICB therapies include:

- CTLA-4: ipilimumab (advanced melanoma)
- PD-1: nivolumab (multiple cancers); pembrolizumab (multiple cancers), cemiplimab (advanced squamous cell, basal cell, non-small-cell lung cancers)
- PD-L1: atezolizumab (advanced lung and urothelial cancers); durvalumab (advanced urothelial cancer); avelumab (advanced urothelial, Merkell cell, renal cell carcinoma)

(See Figure 1.5).

1.3.4.3.2. Adoptive Cell Transfer (ACT) Therapy

Adoptive cell transfer exploits the antitumor properties of lymphocytes directly. This therapy involves isolating lymphocytes from peripheral blood, lymph nodes, or tumor tissue, growing these in culture, and reinfusing them back to the patient. The principle behind the process is to break the tolerance to tumor antigens and produce high avidity effector T-cells to fight the tumor. There are three types of ACT therapy that are under study:

1. ACT with tumor-infiltrating lymphocytes (TIL)
2. ACT with T-cell receptor antigens (TCR)
3. ACT with chimeric antigen receptors T-cell (CAR-T)

Of these, CAR-T is probably the most widely studied and used clinically (see Figure 1.6). ACT with CAR-T uses T-cells that have been genetically modified to directly recognize a specific tumor antigen. Here, a sequence for a particular antibody that targets a specific tumor antigen is added to a viral vector, along with the sequence for other necessary elements for T-cell activation. These are called chimeric antigen receptors and consist of a variable Ig domain (designed to recognize the tumor antigen of interest) fused to a constant T-cell receptor (TCR) domain.

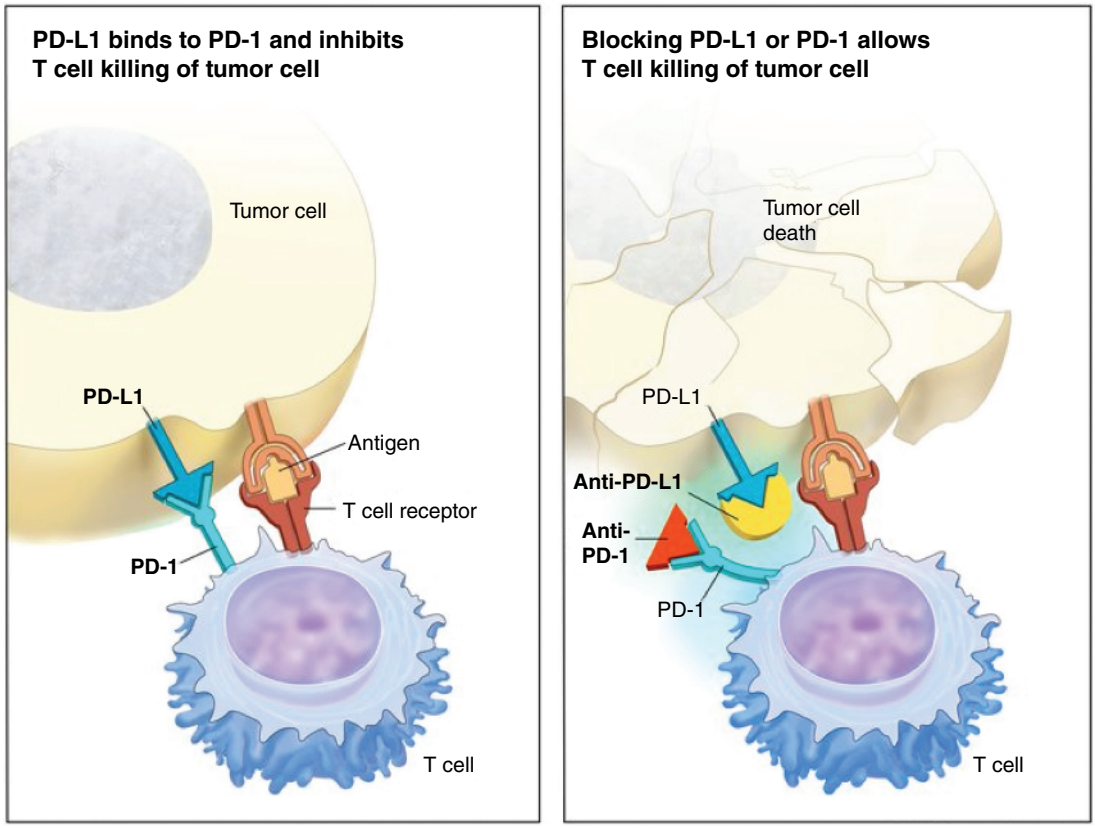

FIGURE 1.5. Mechanism of anti-PD-L1/PD-1 therapy. *Source:* Terese Winslow; National Cancer Institute.

The expression of this tumor antigen on the tumor cell itself is what drives the immune response in this situation.

ACT with CAR-T has limitations due to a lack of highly specific target antigens, lack of durable responses, and the possibility of serious adverse side effects, including cytokine release syndrome. Cytokine release syndrome or cytokine storm is a severe reaction to CAR-T cell therapy that includes high fever, extreme fatigue, difficulty breathing, and a sharp drop in blood pressure. Secondary effects can involve the nervous system. Most often these will subside in patients but treatment with steroids is sometimes needed.

Another limitation of CAR-T therapy is that the process of obtaining and manipulating these T-cells is technically challenging and labor-intensive, thus requiring a highly skilled team. This can make it difficult for eligible patients to access this type of treatment.

At present, there are six FDA-approved drugs for CAR-T therapy (https://hillman.upmc.com/mario-lemieux-center/treatment/car-t-cell-therapy/fda-approved-therapies).

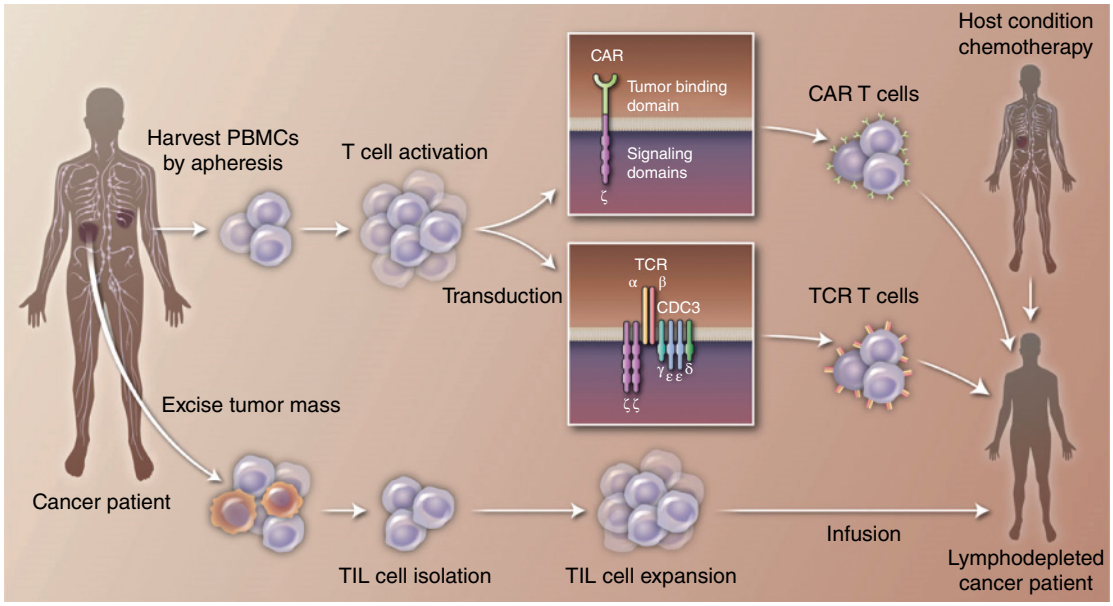

FIGURE 1.6. ACT therapy. Adoptive cell therapy is currently represented by three general approaches. TILs are produced after surgical excision of tumor and enrichment and expansion of TILs from a disaggregated tumor biopsy sample. TCR- and CAR-modified T-cells are produced from peripheral blood lymphocytes in a manufacturing step that includes introduction of the desired receptor through viral or nonviral methods in order to engineer cells. Patients often receive a lymphodepleting chemotherapy regimen before infusion. PBMCs are peripheral blood mononuclear cells. *Source:* June et al. (2015). With permission of the American Association for the Advancement of Science.

1.3.4.3.3. Bispecific Antibody T-Cell Engagers

Bispecific antibody T-cell engagers usually target CD3 on a T-cell and a tumor antigen together. Since CD3 helps mediate T-cell activation, this type of treatment helps recruit and promote T-cell response to tumors. One example of this type of therapy is blinatumomab in the treatment of B-ALL.

1.3.4.3.4. Oncolytic Virus Therapy

Oncolytic virus (OV) therapy involves the use of native or engineered viruses that selectively replicate in and destroy cancer cells. One of the major difficulties of OV therapy is the ability to deliver enough virus effectively into tumor cells, especially for metastatic disease. Consequently, these are not widely used clinically.

1.3.4.3.5. Cancer Vaccines

Cancer cells create an environment that suppresses the immune response. The effectiveness of a therapeutic vaccine depends on breaking the "immune tolerance" to tumor. Challenges to this

include antigen selection and eliciting a robust anti-tumor immune response. Cancer vaccines are considered experimental at this time.

In principle, cancer vaccines might also be able to prevent cancer in high-risk individuals. One area that has quietly been gaining steam is that of a cancer-preventive vaccine for Lynch syndrome. Groups in Europe have been studying neoantigen peptide vaccines for a number of years, and the first clinical trials for a preventive vaccine are planned in the United States in 2022 (https://prevention.cancer.gov/news-and-events/blog/vaccine-prevent-hereditary).

Examples of more traditionally based cancer preventive vaccines include HPV and Hepatitis B vaccines, which indirectly help prevent cervical and liver cancer respectively.

1.3.4.3.6. Gene Therapy

Gene therapy for cancer involves introducing genes back into the tumor cells through a viral vector to help regain control of growth regulation. Examples of this would be to introduce a functioning *TP53* back into tumor cells to reproduce p53's tumor suppressor effect. Other types of gene therapy reintroduce wild-type oncogenes or genes that make the tumor cells more susceptible to the immune response or to chemotherapy/radiation. Another method involves the introduction of a "suicide gene" into the cancer to destroy these cells. Side effects of gene therapy can include severe immune responses and liver toxicities, and other consequences have also been reported. Therapeutic applications of this are experimental.

1.3.4.4. Angiogenesis Inhibitors

Angiogenesis inhibitors (AGIs) are drugs that target blood vessel formation to tumor cells. Tumor cells generally cannot grow without a nutrient supply and send out signals that stimulate blood vessel growth. One of the best examples of an AGI is a monoclonal antibody that targets vascular endothelial growth factor (VEGF), bevacizumab, which was first approved in 2004.

1.3.4.5. Antibody Drug Conjugates

The premise of antibody drug conjugates (ADCs) is that tumor cells express specific antigens that can be targeted by an antibody coupled with a cytotoxic payload. Examples of ADCs in cancer treatment include: trastuzumab emtansine for Her2 positive breast cancers with an antibody that targets Her2 attached to a microtubule disrupting agent and gemtuzumab ozogamicin for AML with an antibody that targets CD33 attached to a DNA-damaging agent.

1.3.5. Stem Cell Transplantation

Hematologic stem cells have the ability to differentiate into all the different types of mature cells in the circulatory and lymphatic systems. Since the major dose-limiting toxicity of chemotherapy is bone marrow suppression, obtaining stem cells prior to chemotherapy can permit the

administration of higher doses of chemotherapy than would otherwise be possible. Stem cells can then be given back to regenerate the bone marrow and potentially rejuvenate a compromised immune system.

Bone marrow transplantation can be performed for curative or palliative purposes. There are many potential complications of transplantation, including infection, bleeding, mouth sores, hair loss, and, rarely, a complete rejection of the transplanted cells (graft rejection). In allogeneic transplants, there is also the risk of an exuberant immune response mounted against the person's own body cells by the foreign donor stem cells, which is termed "graft versus host disease."

The three main sources of stem cells are the bone marrow, peripheral blood, and the umbilical cord. Most transplants performed today use peripheral blood because the cells are easier to obtain, and the immune system recovers faster than with the more conventional bone marrow transplant. Stem cells are obtained from peripheral blood by artificially stimulating stem cell growth in the bone marrow by the use of growth factors. This causes the crowded bone marrow to release some of the stem cells into the bloodstream. These cells are then removed from the bloodstream through a process called apheresis. The stem cells are then returned to the patient following high-dose chemotherapy and/or radiation treatments.

The umbilical cord is rich with stem cells and may be used for transplant. A family at high risk for childhood cancers may want to store or use their unaffected newborn's cord blood in case a sibling develops cancer.

The two major types of bone marrow transplants are described as follows.

- *Allogeneic transplant*—In an allogeneic transplant, the transplanted stem cells are from a donor who shares similar human leukocyte antigens (HLAs). The HLA-matched donor is typically a sibling or parent. If there are no matches among family members, donor registries can be searched. Such registries have increased the number of potential matched donors, although minority ethnic groups remain underrepresented. Cancer patients who undergo allogeneic transplants face problems with rejection of the stem cells and either acute or chronic graft-versus-host disease. Allogeneic transplants have been successfully used to treat leukemias and lymphomas. As an aside, allogeneic transplants are also used to treat other genetic conditions, including severe combined immune deficiency syndrome and sickle cell disease. In families with hereditary hematologic malignancies, it is important to determine carrier status before transplant occurs for the patient and potential donors.
- *Autologous transplant*—In an autologous transplant, the patient's own stem cells are removed and then returned to the patient after they have been given chemotherapy and/or radiation. The transplanted stem cells have been spared the exposure to the toxic treatments and can be returned to the patient without risk of graft-versus-host disease. Autologous transplants are performed for many types of hematologic and solid tumors, especially in children, although its efficacy in treating solid tumors in adults remains unproven.

1.3.6. Additional Cancer Therapies

Other cancer therapies include cryotherapy, retinoid agents, and thermal therapy.

1.3.6.1. Cryotherapy (also called cryoablation or cryosurgery)

Cryoablation uses extreme cold to freeze the tumor and interrupt its growth process. It is also useful in relieving pain and reducing swelling. In cryoablation, liquid nitrogen is poured or forced into probes that have been inserted into the tumor, killing the cells. This can be used in skin cancers and cervical cancers instead of surgery or for tumors where surgery would be difficult (prostate cancers, bone cancers).

1.3.6.2. Retinoid Agents

All-trans retinoic acid (ATRA) induces differentiation of epithelial cells, thus impairing the tumor's ability to grow. Retinoic acid has been found to be quite effective in treating acute promyelocytic leukemia (APML or APL). Isotretinoin (13-cis retinoic acid) is also used to treat neuroblastoma. Other types of retinoid acids are being studied for treatment uses as well. Side effects can include headache, fever, dry skin and mouth, skin rash, nail changes, nosebleeds, swollen feet, sores in the mouth or throat, itching, irritated eyes, muscle and joint pains, hyperlipidemia, and liver toxicity.

1.3.6.3. Thermal Therapy

Thermal therapy involves the use of superheating to kill cancer cells. One example of thermal therapy includes HIPEC therapy below. Other forms of thermal therapy can use lasers, radio waves, ultrasound, or heated chambers. Side effects can include burns, blisters, and pain if treating skin. Perfusion therapy (such as HIPEC) side effects include swelling, blood clots, bleeding, and damage to normal tissues. Whole-body hyperthermia treatment can cause diarrhea, nausea, and vomiting, as well as more serious side effects such as damage to the heart and blood vessels.

1.3.6.3.1. Hyperthermic Intraperitoneal Chemotherapy

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a type of chemotherapy used to treat cancers that have spread into the peritoneum or abdominal lining. These include mesothelioma, appendiceal (including appendiceal mucinous neoplasm), colorectal, gastric, ovarian, or primary peritoneal carcinoma. Surgeons typically remove the primary tumor as much as possible (cytoreductive surgery) and then flush the peritoneum with saline to remove any particulate matter. Superheated chemotherapy drugs such as cisplatin are given into and removed from the peritoneum through inflow and outflow catheters. This can be done through an open or closed technique. While HIPEC is associated with fewer side effects than systemic chemotherapy, there is controversy about whether it provides a survival benefit for any cancer except ovarian cancers that meet certain criteria.

1.4. Risk Factors for Cancer

One of the most common questions in a cancer genetic counseling session is "Why did I get this cancer?" For genetic counselors, it is important to be able to provide some context for patients about this. All cancers are due to a complex interaction of genetic, environmental, and stochastic effects, and the contribution of each of these factors in the development of cancer is different for every person.

When considering risk factors, one type is intrinsic and that is the mutation rate of cells, which should be similar for all people. Beyond that, nonintrinsic risk factors are made up of endogenous (biological) and exogenous (external) types. Modifiable risk factors are comprised of exposures that are controllable such as cigarette smoking and UV-exposure from the sun. Nonmodifiable risk factors may include age and genetics. There may also be partially modifiable risk factors such as workplace exposures to chemicals (e.g., for firefighters) and geographical location (e.g., pollution). Even biological factors such as rate of inflammation in the body might be partially modifiable. For instance, the use of low-dose aspirin as an anti-inflammatory has been shown to reduce the risk of colorectal cancer for certain people. In the assessment of cancer risk, it is important to determine what risk factors, outside of genetics, may be contributing to cancers in the family.

Patients often ask about what kind of substances cause cancer. Carcinogens are well-studied cancer-causing agents, which can be chemical, physical, or viral. Examples of physical carcinogens include fibrous materials such as asbestos or particulate matter found in the air from pollution, both of which are linked to an increased risk for lung cancer. Ultraviolet radiation found in sunlight is another example of a physical carcinogen. Chemical carcinogens are substances, natural or man-made, that consist of a discrete molecular structure. Most chemical carcinogens are indirect-acting and require metabolic activation to cause cancer, although some are carcinogenic on their own. Examples of direct-acting carcinogens are formaldehye and sulfur mustard, whereas examples of indirect-acting chemical carcinogens are polyaromatic hydrocarbons (PAH) and benzene. Please see the link from the 15th report on carcinogens as determined by the National Toxicology Program for a complete list:

(https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf)

Age, which is nonmodifiable, is the most common risk factor for cancer, with the average age of all cancers combined occurring at age 66. However, the World Health Organization estimates that 30–50% of cancers are preventable. The most common carcinogen is tobacco through cigarette smoking, although any use of tobacco (cigar, snuff, chew) and even secondhand or passive smoke exposure increases the risk for cancer. Other common carcinogens include alcohol, UV exposure (including using tanning beds), and the human papilloma virus (HPV). Workplace exposure to carcinogens is another important area for preventive measures. Occupational exposures to carcinogens in general industry, maritime, and construction are regulated by the occupational health and safety administration (OSHA). For more information on cancer prevention, please see the American Cancer Society's (https://cancer.org/healthy.html) as well as the National Cancer Institute's (https://www.cancer.gov/about-cancer/causes-prevention) websites.

See Table 1.9 for common risk factors and cancer types.

See Table 1.10 for selected carcinogens and the increase in specific cancer risks.

TABLE 1.9. Factors Associated with Increased Cancer Risk by Type

Risk Factor	Cancer Type
Smoking	Oral cavity, pharynx; stomach; colorectum; liver; pancreas; nasal cavity/paranasal sinus; larynx; lung, bronchus, trachea; cervix; kidney, renal pelvis, ureter; urinary bladder; acute myeloid leukemia
Exposure to secondhand smoke	Lung, bronchus, trachea
Excess body weight	Esophagus (adenocarcinoma); stomach (cardia), colorectum; liver; gall bladder; pancreas; female breast; corpus uteri; ovary; kidney, renal pelvis; thyroid; multiple myeloma
Alcohol intake	Lip, oral cavity, pharynx, esophagus (squamous cell carcinoma); colorectum; liver; female breast
Poor diet	
Red meat consumption	Colorectum
Processed meat consumption	Colorectum; stomach (noncardia)
Low fruit/vegetable consumption	Colorectum
Low dietary fiber consumption	Colorectum
Low dietary calcium	Colorectum
Physical inactivity	Colon, excluding rectum; female breast
Ultraviolet radiation	Melanoma of the skin
Infections	
Helicobacter pylori	Stomach
Hepatitis B virus	Liver
Hepatitis C virus	Liver
Human herpes virus type 8; Kaposi sarcoma herpes virus	Kaposi sarcoma
Human immunodeficiency virus	Anus, Kaposi sarcoma, cervix; Hodgkin lymphoma; non-Hodgkin lymphoma
Human papilloma virus	Oral cavity; oropharynx tonsils and base of tongue; anus; cervix; vulva; vagina; penis

Source: Adapted from Islami et al. (2018).

TABLE 1.10. Cancers Associated with Various Occupations or Occupational Exposure

Cancer	Substances or Processes
Lung	Arsenic, asbestos, cadmium, coke oven fumes, chromium compounds, coal gasification, nickel refining, foundry substances, radon, soot, tars, oils, silica
Bladder	Aluminium production, rubber industry, leather industry, 4-aminobiphenyl, benzidine

Continued

TABLE 1.10. Cancers Associated with Various Occupations or Occupational Exposure—*Continued*

Cancer	Substances or Processes
Nasal cavity and sinuses	Formaldehyde, isopropyl alcohol manufacture, mustard gas, nickel refining, leather dust, wood dust
Larynx	Asbestos, isopropyl alcohol, mustard gas
Pharynx	Formaldehyde, mustard gas
Mesothelioma	Asbestos
Lymphatic and hematopoietic	Benzene, ethylene oxide, herbicides, x-radiation system
Skin	Arsenic, coal tars, mineral oils, sunlight
Soft-tissue sarcoma	Chlorophenols, chlorophenoxyl herbicides
Liver	Arsenic, vinyl chloride
Lip	Sunlight

Sources: American Cancer Society Fact Sheet "Occupation and Cancer": International Agency for Research on Cancer.

Source: Agency for Toxic Substances and Disease Registry (ATSDR).

15. Case Examples

1.5.1. Case 1

Case Presentation: The genetic counselor is scheduled to see Joe, age 42, for genetic counseling due to a family history of cancer. There is little information about the exact types of cancers that were found in the family ahead of time. When the genetic counselor meets Joe, he tells the counselor that his father died of cancer a few months ago at age 68, and he is very anxious about the possibility that he will get cancer too. Joe tells the counselor that his father had liver cancer and then goes on to say that "he was a heavy drinker, though, and I only drink a lot on the weekends."

As the genetic counselor starts to take the family history, Joe describes that he has two uncles who also died of cancer in their 50s, both of whom were also heavy drinkers. He then reports that he has a cousin on his father's side who recently developed "a female cancer" at age 35. Joe goes on to state that his grandparents on his father's side both died in their 50s in a car accident, and his father, as the oldest child, was responsible for taking care of his younger siblings as young adults. While Joe is an only child, he does worry about his three young children and what would happen to them if he should die of cancer at a young age.

The genetic counselor begins to discuss the family history with him and asks whether Joe knows if the liver cancer was the primary tumor or whether the cancer had spread to the liver from somewhere else. Joe considers this and says that he believes his father may have had colon cancer before but that he had surgery so "it was taken care of." The counselor gently probes about whether his dad might have had a recurrence of the colon cancer and that it might have spread to the liver. Joe says he can ask his mother about this, although he is not sure about bringing up his father's cancer again so soon after his death. The counselor also asks whether it would be possible to talk to his cousins to see if there is more information about his uncles' and living

cousins' diagnoses. Joe states that he has one cousin he is very close to who could probably tell him about the family cancer history.

The genetic counselor reviews the possible scenarios based on the pattern of cancer in the family. Unfortunately, without knowing the types of cancers, it is difficult to assess the family history. It is possible that Joe is right and that if his father and uncles had liver cancer, alcohol may have played a significant role in the development of their cancers. If his paternal first cousin's diagnosis of cancer was actually cervical cancer, this is less likely to be related to a strong inherited susceptibility. However, it is also possible that his father and two uncles may have had a primary colon or other gastrointestinal cancer and that his cousin had an early uterine or ovarian cancer, which would raise the question of Lynch syndrome. The genetic counselor asks Joe if he would be willing to do some legwork in trying to sort through the diagnoses. Joe states that he would be willing to do that.

Follow-Up: Joe calls the genetic counselor within a couple of weeks to let her know that his dad indeed had colon cancer that spread to the liver. He had been treated at a different hospital when he was younger, and he died so quickly after being diagnosed with the liver cancer that the hospital hadn't had a chance to do any biopsies for molecular studies on the tumor. After a discussion with the cousin he was close to, he found out that his female cousin had been diagnosed with uterine cancer. She was undergoing genetic testing with her providers locally, but her doctors had mentioned Lynch syndrome to her as well.

About a month later, Joe called the genetic counselor back and said that his cousin shared her test report with him. She was found to have a pathogenic variant in the *MLH1* gene. The genetic counselor arranged for Joe to have genetic testing through a multi-gene cancer panel, and he was found to be negative for the *MLH1* pathogenic variant as well as for other mutations. Joe was very happy to hear that he did not have the familial pathogenic variant. The counselor also gave him information about steps to be healthy and prevent cancer outside of hereditary risk, and he was more than willing to work with his doctor to reduce his risk and stay on top of screening.

Case Discussion: This case illustrates the importance of obtaining accurate family cancer history information, especially regarding primary cancer versus metastatic disease. While it is likely that Joe's father had the *MLH1* pathogenic variant, since there is no way of verifying this, Joe's testing included other genes to rule out common cancer syndromes. The contribution of alcohol use to the risk of cancer in this family may still be an important risk factor even in the context of a hereditary syndrome. Joe's drinking, while not as heavy as his father's, is still relevant for him as a risk factor for cancer in general, and encouraging a healthy lifestyle is a responsibility for all of his providers. The genetic counselor was also able to be reassuring about the risks of hereditary cancer for his children.

1.5.2. Case 2

Case Presentation: A 35-year-old patient, Claudia, is seen for genetic counseling to discuss her family history of blood cancers. The genetic counselor begins by reviewing what will happen during the course of the session. They outline that they will be taking a family history of cancer,

going over her personal medical history, assessing for genetic risk, and discussing genetic testing options if relevant. They start out by asking if she has any questions or concerns about the session. Claudia states that she is not too worried about the family history and that her sister's doctor has recommended that she be seen in genetics but was unsure why.

The genetic counselor takes the family history and learns that Claudia's sister was diagnosed with some kind of precancerous blood condition at age 35 and that her doctors are concerned that she now has a type of blood cancer at age 37. Her sister is being treated across the country in California, and her doctors are looking for a potential donor for a stem cell transplant. It was determined that Claudia and one of her brothers could possibly be donors. The only other cancer that Claudia knows of is of a cousin who died at age 32 of leukemia. Claudia's mother and father did not have cancer and died in their 70s of heart-related issues. She knows that her mother as well as several aunts in Brazil had bleeding problems, and her father had two brothers who died of heart disease. She is not in touch with her relatives there. She and her brother are younger than her sister with cancer.

The genetic counselor explains to Claudia that there may be concern for hereditary risk due to her sister's cancer. The first step in trying to understand the risk for Claudia is to obtain more information about her sister's diagnosis. Claudia is able to call her sister during the session and learns that her sister was diagnosed with myelodysplastic syndrome at age 35 and now the doctors think that she has acute myeloid leukemia (AML). The genetic counselor discusses that it would first be better to try to test her sister for pathogenic variants in genes that predisposed to AML if possible. Claudia learns that her sister underwent a skin biopsy for genetic testing when she was going in for a bone marrow biopsy a couple of weeks ago. Results of the genetic testing on her sister are not back yet. Since it can take some time for these results to come back and figuring out Claudia's own risk was essential to determining whether she could be a possible donor, the counselor suggests that Claudia have her blood drawn and sent off to the laboratory for testing of a broad panel of genes related to susceptibility for AML; the laboratory would allow the counselor to order specific site testing at a later date if her sister's testing indicated that she had a pathogenic variant in a gene that had not been tested.

The counselor suggests that her brother, Carlos, who could also be a potential donor, come in for genetic counseling soon. Claudia calls him, and he is scheduled to be seen the next day. The counselor has a good conversation with Claudia about the possibility of finding out that she has risk for hematologic malignancies and the uncertainties of how best to follow and treat patients in this situation. Additionally, the counselor takes a detailed history related to other conditions that can sometimes be seen with AML.

Follow-Up: Claudia's test results come back negative for pathogenic variants in the genes for which she was tested. Her brother's results take a few days longer and, in that time, her sister's testing comes back showing that she has a pathogenic variant in the *RUNX1* gene. Claudia finds out through her brother that two maternal aunts had bleeding disorders and one maternal aunt died of leukemia in Brazil. Her brother's testing eventually comes back showing that he also has the same *RUNX1* pathogenic variant as their sister. Claudia's testing included the *RUNX1* gene, and, since she tested negative, she is able to donate stem cells for her sister shortly after this. Because she is a matched related donor, her sister did well after transplant. The family is evaluated for platelet disorders and other issues related to the *RUNX1* mutation.

Case Discussion: In this case, it was very important for the genetic counselor to have accurate information about the diagnosis and testing information so that appropriate testing could be done. Rapid testing was essential to determine whether Claudia was an eligible donor for her sister. The knowledge of other conditions in the family such as the report of bleeding disorders was also important for assessment.

1.6. Discussion Questions

Question 1: You are seeing a 45-year-old assigned female at birth patient who has a family history of pancreatic cancer. She has a mother and maternal aunt who were both diagnosed with pancreatic cancer, her mother at age 60 and maternal aunt at age 65. Her mother passed away shortly after diagnosis, but her aunt has been put on a targeted therapy that seems to be working.

a. If the patient asks about what the main warning signs are for this cancer, what would you say?
b. What are the risk factors for pancreatic cancer that might be relevant for her?
c. What kinds of targeted therapy could her aunt be on?

Question 2: A patient is added to your schedule on the same day she is having radiation treatment for breast cancer. She has completed 2 weeks of treatment.

a. How might the side effects of treatment affect your interaction with the patient during a genetic counseling session?
b. She has already undergone surgery to remove the primary tumor. What terminology would you use to describe the treatment she is having now?
c. What would you look for her in pathology report that could help you in assessing hereditary risk?

1.7. Further Reading

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