1.0 A History of Rare Diseases in the United States

An axiom taught in medical schools around the world goes like this: When you hear hoofbeats, think horses, not zebras. We don’t want future physicians thinking about the most fanciful possibilities when they see a patient. We want them to start with the most obvious diagnosis. Many potential diagnoses are so rare that most doctors will never see a patient with any of them. Rare diseases (that is, the zebras) do occur, though, and physicians must keep them in the back of their minds as they try to determine what is actually wrong with their patients. This is why the Office of Rare Diseases Research has unofficially adopted the zebra as its mascot.

In the United States, a disease is considered rare if it affects fewer than 200,000 Americans (Institute of Medicine (IOM), 2010). Some rare diseases, such as cystic fibrosis and Tourette's syndrome, are relatively well known to the public, but most are not. About 7,000 rare diseases have been identified, and researchers continue to describe new ones. Many affect fewer than 1,000 people in the United States, but taken together, they represent a significant health concern affecting an estimated 25 million (ORDR, 2009). The majority of rare diseases are caused by gene mutations, but they can also be caused by infection from pathogens and exposure to environmental toxins.

A smaller number of diseases are called “neglected diseases.” This term is often applied to tropical infections that are overwhelmingly concentrated in the world's poorest countries. Examples of neglected diseases include the following:

- Leishmaniasis, a parasitic disease affecting about 12 million people worldwide and found, rarely, in the United States among people who have been traveling (World Health Organization, 2009).
- Dengue fever, a disease caused by a virus transmitted through a mosquito bite. It affects about 50 million to 100 million people worldwide but is very rare in the United States (Centers for Disease Control and Prevention (CDC), 2009).
- Schistosomiasis, a parasitic disease affecting multiple organs. It affects an estimated 200 million people worldwide and is not found in the United States (CDC, 2008).

A disease is sometimes described as having a trajectory, meaning that the number of people affected by the disease changes through time. This means that a rare disease may become common, and a common disease may become rare. For example, AIDS was once a rare disease, but as HIV infection spread around the world, it became a common disease. Effective disease prevention programs can turn a once-common disease into a rare one. This has happened to diseases such as measles and mumps through childhood vaccination programs. Healthcare professionals are concerned that some currently rare diseases may become common due to the spread of drug-resistant pathogens and public opposition to childhood vaccinations (IOM, 2010).
Patients and their families dealing with rare diseases face obstacles beyond coping with the diseases themselves (Rados, 2003):

- Many patients experience the frustration of not being able to obtain an accurate diagnosis. For approximately one-third of patients with a rare disease, correct diagnosis takes between one and five years. In Europe, researchers analyzed surveys from over 6,000 patients involving eight rare diseases, including Marfan syndrome, cystic fibrosis, and Duchenne's muscular dystrophy. Over 40 percent of the respondents indicated that their first diagnosis was wrong, and 25 percent reported that it took between 5 and 30 years to obtain a correct diagnosis (Faurisson, 2004).

- Patients often feel isolated and don't know anyone else who is dealing with the same disease.

- Many patients must travel long distances to reach appropriate medical care.

- The cost of diagnosis and treatment can be very expensive.

- There may be no medications or other treatments for the disease.

Until the mid-1980s or so, the study of rare diseases was a low priority for the medical community. Since then, however, researchers have focused more attention on rare diseases for reasons we explain below. The increased visibility of rare diseases and resources devoted to them gave us the opportunity to develop a curriculum supplement that allows students to gain an understanding of the concept of rare diseases and how they are studied. To appreciate the advances made in the area of rare diseases since 1980, it’s helpful to look at a brief history of the field.

Because each rare disease affects so few people, pharmaceutical companies reasoned that it was not cost effective to develop drugs to treat them. Because those companies were not interested in “adopting” the research needed to develop drugs, the lack of attention to rare diseases led to the terms “orphan diseases” and, for the drugs needed to treat them, “orphan drugs.” In the United States, this situation began to change in the 1980s. The Food and Drug Administration (FDA) established the Office of Orphan Products Development (OOPD). Its aim is to identify and support the development of orphan drugs and biologic products needed to treat rare diseases. To carry out its mission, the OOPD works in collaboration with other stakeholders such as the research community, academia, rare disease organizations, and pharmaceutical companies.

Congress passed the Orphan Drug Act (ODA) in 1983. The ODA helps foster the development of orphan drugs by providing financial incentives

Figure 1. Congress stimulated research on rare diseases by passing the Orphan Drug Act.
to pharmaceutical companies. A medication that has orphan drug status must meet the same safety and efficacy standards as other drugs. A company working on an orphan drug receives tax credits and a seven-year period to exclusively market the drug when it's ready. In the 10 years before the ODA, only 10 drugs aimed at rare diseases were privately developed. Since then, the FDA has approved more than 350 orphan drug applications. Drugs aimed at rare diseases accounted for over 30 percent of the innovative drug applications approved by the FDA from 2004 to 2008 (Coté, 2009).

Medical devices intended to treat patients with rare diseases are not clearly addressed by the ODA. In 1996, the FDA created the Humanitarian Device Exemption (HDE) provision of the Safe Medical Devices Act of 1990. It allows the expedited approval of a medical device for treating a rare disease provided that the device is safe and is likely to benefit patients. This approval can be granted without costly clinical studies. From 1996 to 2003, the OOPD gave out 32 HDEs (Rados, 2003). One example of where the provision has had an impact is in the rare placental disorder twin-to-twin transfusion syndrome. Blood vessels often connect the circulation of developing twins, and sometimes this leads to one twin receiving more blood flow than the other. A device approved through the HDE provision allows physicians to identify blood vessels that connect the twins in utero and then normalize the blood flow in those vessels (National Organization for Rare Disorders, 2011).

The Rare Diseases Act of 2002 established the Office of Rare Diseases (ORD) at NIH to provide information on rare diseases, including their diagnosis and treatment, and help establish links among investigators, patients, and research subjects. The Office's focus on research soon prompted a name change to the Office of Rare Diseases Research (ORDR). ORDR staff work to identify rare diseases where research is lacking and to support research in those areas. In 2003, ORDR helped fund the Rare Diseases Clinical Research Network (RDCRN). It consisted originally of 10 research consortia and a Data and Technology Coordinating Center; by 2009, the Network had grown to 19 consortia plus a Data Management and Coordination Center. The network has conducted or is conducting about 100 studies across the United States and several other countries. Each consortium focuses on a group of medically related rare diseases.

Although many rare diseases have no effective treatment options, medical research is producing tangible benefits for many patients and their families. During the 1960s, people with cystic fibrosis had a life expectancy of fewer than 10 years. Today, people with the disease can expect to live to nearly 40 years (Cystic Fibrosis Foundation, 2008). A 2008 review of treatments for 65 rare diseases revealed that between 1983 and 2008,

• the number of diseases with no treatment options decreased from 31 to 17 and
• the number of diseases that fully responded to treatment increased from 8 to 20 (Campeau et al.).

Attention to rare diseases has grown since the 1980s through the efforts of nonprofit organizations and foundations, some of which were created by people affected by rare diseases (Rados, 2003). For example, Brad and Vicki Margus had two boys with ataxia-telangiectasia (A-T), a fatal genetic disorder that involves the loss of motor control, among other symptoms. Brad left his business to start the A-T Children's Project, a nonprofit organization aimed at isolating the gene responsible for A-T and providing support for affected families. His efforts were rewarded in 1995, when a scientist supported by funds from the A-T Children's Project identified the gene (called ATM) associated with the disease (Savitsky et al., 1995). It turned out that the ATM gene codes for a protein that helps mediate a cell's response to DNA damage by regulating its progression through the cell cycle. The isolation of the ATM gene not only helped researchers better
understand the cause of this rare disease, but it shed light on a mechanism of cancer.

Research on a rare disease often produces findings that provide insight into more-common diseases. For example, Wilms' tumor (a rare pediatric cancer) research has been cited as a model for understanding the genetics and molecular biology of pediatric cancers in general (Feinberg and Williams, 2003). Research into Tangier disease (a very rare disease associated with improper cholesterol processing) identified a target for therapy to lower the risk for heart disease and provided insight into Alzheimer's disease (Delude, 2009). In other cases, research findings have helped prevent a rare disease. For example, women can follow simple nutritional measures to reduce the incidence of birth defects such as spina bifida in their children.

Many of the same patients and families who lobbied for the passage of the Orphan Drug Act worked to create a nonprofit organization that would address their needs. Founded in 1983, the National Organization for Rare Disorders (NORD) provides information about diseases, referrals to patient organizations, research grants, and advocacy for the rare diseases community.

2.0 The Impact of Genomics on Rare Diseases

Most rare diseases are caused by genetic mutations or variations. In fact, we now think that 80 percent or more of rare diseases have a genetic cause (NIH, 2010; NORD, 2007). This means that we can use genetics and rare diseases in a curriculum supplement to address concepts such as these:

- Some rare diseases are more prevalent in certain groups.
- Inherited and environmental factors affect the function of an organism and may contribute to the occurrence of rare diseases.
- People affected by inherited rare diseases should not be stigmatized.
- People affected by inherited rare diseases can lead meaningful lives.

To help provide information on genetics and rare diseases, the National Human Genome Research Institute and ORDR established the Genetic and Rare Diseases Information Center in 2002. The next year, the completion of the Human Genome Project (HGP) opened the floodgates on a torrent of human genetic data. Once the reference sequence was finished, it became clear that the human genome contained fewer genes than originally expected—about 25,000 total. After scientists had established the approximate number of human genes, they turned their attention to assessing the amount of genetic variation among human populations. The aim is to associate specific genetic variations with diseases, both common and rare. As seen in the following graph (Figure 2), the pace of disease-gene discovery shows no sign of leveling off (McKusick-Nathans Institute et al., 2005).

Soon after scientists began to explore genes related to disease through the HGP, NIH began researching human genetic variation through the International HapMap Project. Data from the HGP indicated that the genomes of any two humans are, amazingly, more than 99 percent the same. This observation also means that any two individuals have several million differences in their genomes.

The most common type of genetic variation is called a single nucleotide polymorphism (SNP, pronounced “snip”). A SNP is a place in the genome where individuals may vary by a single base pair. The human genome contains more than 10 million different SNPs (International HapMap Consortium, 2007). SNPs that are clustered close together on the chromosome are inherited together as a single unit, or haplotype. The International HapMap Project used DNA samples from people of diverse ethnic backgrounds to assemble a map of these haplotype blocks.

The International HapMap Project, completed in 2005, produced a map containing data on more than 1.3 million SNPs (International HapMap Consortium, 2005). Scientists immediately used HapMap data to conduct genome-wide association studies, in which genomes from many people are rapidly scanned to identify
SNPs associated with diseases. Once the scientists characterize the disease-associated SNPs, they can use the data to help prevent, diagnose, and treat diseases. Within two years, HapMap data helped identify more than 50 genes associated with diseases, including type 2 diabetes, Crohn’s disease, elevated cholesterol, rheumatoid arthritis, multiple sclerosis, and prostate cancer (Massachusetts General Hospital, 2007).

The completion of the International HapMap Project did not stop the exploration of human genetic variation. In 2007, a second-generation human haplotype map was assembled containing data on over 3.1 million SNPs (International HapMap Consortium, 2007). This second map, with its increased density of SNPs, allows researchers to identify recently inherited chromosomal segments that may hold a key to understanding rare disease–associated variations that until now have been very difficult to detect.

The single base variations associated with the HapMap Project are not the only types of genetic variation associated with disease. Structural variations involving thousands of bases of DNA sequence are also being investigated. Such structural variations are associated with variation in gene expression (Stranger et al., 2007), female infertility (Stefansson et al., 2005), susceptibility to HIV infection (Gonzalez et al., 2005), systemic autoimmunity (Fanciulli et al., 2007), and genetic disorders such as Williams-Beuren syndrome and velocardiofacial syndrome (Freeman et al., 2006; Lupski and Stankiewicz, 2005).

Some rare diseases are caused by simple genetic mutations or variations and can serve as good examples for middle school students learning about a disease and its biological functions as well as the fundamentals of genetics. The inheritance of single-gene diseases is relatively simple. The more-common single-gene disorders include the following:

- sickle cell disease: A recessive disorder in which affected people produce abnormal hemoglobin.
- cystic fibrosis: A recessive disorder in which the body produces thick, sticky mucus that clogs the lungs and leads to infections. It is the most common fatal genetic disease in the United States.
Tay-Sachs disease: A recessive disorder that results in the progressive destruction of the nervous system in children. After genetic testing and community counseling programs became available in 1970, the incidence of Tay-Sachs disease in the United States and Canada decreased by 90 percent in the Jewish population most at risk for the disease (Kaback et al., 1993).

Huntington’s disease: An autosomal dominant disorder that usually appears during middle age and leads to progressive loss of control over movement and intellectual faculties.

Today, about 1,500 different tests are available to detect mutations associated with genetic diseases. This number may seem large, but it falls well short of the number of rare diseases thought to have genetic causes (National Center for Biotechnology Information, 2009). Many of these genetic tests are offered by just a few laboratories across the country. Furthermore, the tests may be expensive and may not be covered by medical insurance.

3.0 Rare Infectious Diseases

Some rare diseases are caused by infection with a pathogen. Rare diseases spread by pathogens have the potential to become common diseases, provided that conditions promoting transmission are present. The spread of AIDS illustrates how a once rare disease (because it was new) can become common in a relatively short time.

One class of rare diseases is associated with an unusual type of infectious agent called prions, which are thought to consist entirely of protein and to lack the DNA or RNA genome found in viruses. The term prion was coined by Stanley Prusiner in 1982 to describe proteinaceous infectious particles associated with diseases such as scrapie in sheep, bovine spongiform encephalopathy (mad cow disease) in cattle, and Creutzfeldt-Jakob disease in humans.

The infectious nature of prions in humans was first observed among the Fore people living in the highlands of New Guinea in the 1950s. Women and children were dying from a progressive brain disease called kuru by the local people. Research by Carleton Gajdusek established that the infectious agent, then thought to be a conventional virus, was being transmitted through the practice of cannibalism (Gajdusek et al., 1967).

All prion diseases characterized so far affect the structure of the brain or other neural tissues and are untreatable and fatal. The prion particle is derived from a protein that is a normal part of the central nervous system. For reasons unknown, the normal protein, PrP, sometimes misfolds, and in its new conformational state is able to induce other PrP molecules to do the same. This wave of PrP molecules turning into prions becomes an assault on the brain, thus producing the disease symptoms.

There are many unanswered questions about prions, including, what’s the role of the PrP protein in the cell? Two recent studies suggest a possibility to explore (Steele et al., 2006; Zhang et al., 2006). We know that although prion diseases exclusively affect the nervous system, the PrP protein is found throughout the body. The two studies show that the PrP protein is expressed on the surface of stem cells in the bone marrow and on cells that become neurons. In both cases, PrP seems to support the ability of the cells to mature and divide. Establishing the normal role for PrP should open new avenues for understanding and, ultimately, treating this rare but devastating class of diseases. As research into infectious diseases continues, the goal is to make the common diseases rare and the rare diseases extinct.
4.0 Rare Diseases Caused by Environmental Toxins

Some rare diseases result not from faulty genes or infection by pathogens, but from exposure to toxins or other extrinsic factors in the environment. As with infectious diseases, those caused by exposure to environmental toxins may be either common or rare, and the rare ones have the potential to become common.

Harmful extrinsic factors may be of natural or human origin. Natural factors include ionizing radiation (from sunlight or elements such as radon), heavy metals (such as lead and mercury), and chemicals produced by organisms. Many plants produce chemicals that function as pesticides. Other plant toxins are produced in response to stresses caused by severe weather, ultraviolet light, and infection by microbes.

Some of the most potent naturally occurring toxins are produced by microorganisms. Botulinum, for example, is produced by the bacterium *Clostridium botulinum* and causes the rare disease botulism. Most cases of botulism involve eating food contaminated with preformed botulinum neurotoxin. In rare cases, called colonization botulism, a person eats food containing spores of *C. botulinum*. The spores germinate inside the body, resulting in a colony of bacteria that then produce the toxin. The appearance of colonization botulism is associated with certain risk factors, most commonly the digestive disorder Crohn’s disease (Health Canada, 2007).

Other rare diseases are caused by exposure to industrial chemicals. This can happen as a result of lifestyle choices (such as smoking) or living or working in a harmful environment. Some industrial chemicals are strongly associated with specific diseases. For example, virtually all cases of mesothelioma are attributed to exposure to asbestos. Table 9 lists several harmful industrial chemicals and the diseases that result from exposure to them.

Although the causes of rare diseases can be classified as genetic or environmental, many of the diseases are, in fact, multifactorial, meaning that they result from interactions between genetic and environmental factors. Since the HGP was completed in 2003, researchers have been working to establish the genes’ functions and relationships to both health and disease.

Some scientists are exploring how the interaction of genes and environmental factors produces disease. For example, Michael Borchers has been investigating a receptor protein called NKG2D found on the surface of lung cells (Borchers et al., 2006). Normally, the NKG2D protein helps the immune system attack and destroy lung tissue damage caused by infection from a pathogen. However, when the lungs experience chronic low-level damage from environmental toxins through smoking or exposure in the workplace, the amount of tissue damage may exceed the body’s ability to repair it. In such cases, the activity of NKG2D is unwanted because it stimulates the immune system to attack the affected tissue—and contributes to chronic lung disease instead providing

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**Table 9. Industrial Chemicals and Their Associated Diseases**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Disease(s)</th>
</tr>
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<tbody>
<tr>
<td>Asbestos</td>
<td>Asbestosis; mesothelioma</td>
</tr>
<tr>
<td>Beryllium</td>
<td>Chronic beryllium disease</td>
</tr>
<tr>
<td>Coal dust</td>
<td>Pneumoconiosis</td>
</tr>
<tr>
<td>Cotton dust</td>
<td>Byssinosis</td>
</tr>
<tr>
<td>Dioxins, polychlorinated biphenyls (PCBs)</td>
<td>Chloracne</td>
</tr>
<tr>
<td>Nylon flocking</td>
<td>Flock worker’s lung</td>
</tr>
<tr>
<td>Silica</td>
<td>Silicosis</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Welding fumes</td>
<td>Metal fume fever</td>
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</table>

Borchers believes that by blocking the activity of NKG2D, he can stop this immune response and minimize damage to the lungs (University of Cincinnati, 2006).

Other causes of rare diseases include:
- nutritional deficiency: for example, beriberi results from a lack of thiamine;
- injury: for example, commotion cordis is associated with ventricular fibrillation and sudden death, which result from a nonpenetrating blow to the chest; and
- a treatment for another disease: for example, radiation is often used as a cancer treatment, but it may also cause radiation-induced meningioma (a rare central nervous system tumor).

5.0 Rare Diseases Featured in This Curriculum Supplement

5.1 Necrotizing Fasciitis

Necrotizing fasciitis (NF) is a bacterial infection. The bacteria attack the soft tissue and the fascia, a sheath of tissue that covers muscles. Most commonly, the infection is from Group A Streptococcus bacteria strains. This is the same kind of bacteria responsible for causing strep throat. Most strep strains are easily killed by antibiotics. Some are not, though, and, under the right set of conditions, can cause NF. These conditions include the following:
- An opening in the skin through which the bacteria enter the body. The opening can be large, as a result of trauma or surgery, or very small, as from a pinprick or paper cut.
- Contact with the bacteria, either from inside the person or from another infected person.
- Infection by an invasive strain of the Group A Streptococcus bacteria.

After the bacteria enter the body, they reproduce quickly and release toxins and enzymes that destroy soft tissue and fascia. The dead tissue must be removed to save the patient’s life. The bacteria are able to elude the body’s immune system and spread through different tissue layers. In addition to the tissue damage, the infection can result in toxic shock, which is characterized by a drop in blood pressure; a weak, rapid pulse; fever; dizziness and confusion; and difficulty breathing.
Fortunately, NF is rare, although accurate statistics are hard to find. In 1996, the CDC estimated that there were between 500 and 1,500 cases of NF in the United States and that 20 percent of these resulted in death (National Necrotizing Fasciitis Foundation (NNFF), 2009).

**Symptoms of NF:** NF produces flu-like symptoms, so people initially believe that they simply have the flu. Misdiagnosis is common, which can have devastating consequences because the bacterial infection advances so fast. The symptoms of NF progress as follows (NNFF, 2009):

**Early symptoms (usually within the first 24 hours)**
- An opening in the skin (from even a slight trauma) has appeared, allowing the bacteria to enter the body.
- The patient feels discomfort in the general area of the trauma.
- The pain increases out of proportion to the injury.
- Flu-like symptoms appear such as vomiting, diarrhea, dehydration, fatigue, weakness, muscle pain, and fever.
- Intense thirst develops as the body dehydrates.

**Advanced symptoms (usually within three to four days)**
- The painful area of the body begins to swell and may show a purplish rash.
- The painful area may develop large, dark blisters.
- The wound may take on a bluish, white, or dark, mottled, flaky appearance.

**Critical symptoms (usually within four to five days)**
- Blood pressure drops severely.
- Heartbeat increases.
- A rash may appear over the body, caused by toxins released by the bacteria.
- Toxic shock causes the body’s organs to shut down.
- Unconsciousness results as the body becomes too weak to fight the infection.

**Treatment of NF:** NF requires treatment at a hospital. The patient is given intravenous antibiotics, and the infected tissue is removed. Depending on the severity of symptoms, other treatments may be needed, such as blood transfusions and medications to raise blood pressure and boost the immune system.

**Surviving NF:** Patients surviving NF may be left with minimal to severe scarring. Almost all patients need to have at least some skin removed. As a result, they may have to undergo a series of skin grafts. In some cases, amputation of an affected limb is necessary.

**5.2 Marfan Syndrome**
Marfan syndrome is a genetic disease of the connective tissue. It’s caused by mutations in the gene that codes for the connective tissue protein fibrillin-1. As a result of the mutated fibrillin-1 gene, another protein called “transforming growth factor beta” (TGFβ) increases in concentration, causing certain connective tissue problems. The Marfan syndrome phenotype is inherited as an autosomal dominant trait. This means that a single copy of the mutated gene is enough to cause the disorder. It also means that an affected person has a 50 percent chance of passing on the disorder to each child. The syndrome is mostly an inherited condition, but in about 25 percent of cases, it’s caused by a spontaneous mutation in a sperm or egg.
cell of an unaffected parent (Dietz, 2009). The National Marfan Foundation estimates that about 200,000 people in the United States are living with Marfan syndrome or a related connective tissue disorder (National Marfan Foundation, 2011).

**Features of Marfan Syndrome:** People with Marfan syndrome have the genetic mutation in all their cells. This means that the disorder affects the connective tissue in many different body systems. The medical features associated with Marfan syndrome appear at all ages, including in infants and small children. Some of the most common features of Marfan syndrome are listed below (Table 10). With early diagnosis, proper treatment, and careful management, it’s possible for people with Marfan syndrome to live a normal life span.

**Diagnosis of Marfan Syndrome:** The connective tissue problems associated with Marfan syndrome can affect multiple body systems. This can complicate diagnosis of the disorder. Doctors may treat patients with the syndrome for several medical problems at once without realizing that they stem from a single cause. Although we know that Marfan syndrome is caused by mutations in the *fibrillin-1* gene on chromosome 15, there’s no simple blood test that can diagnose the disorder. Instead, doctors have established a set of diagnostic criteria to use. These criteria span various body systems and are classified as either major or minor.

**Table 10. Features of Marfan Syndrome**

<table>
<thead>
<tr>
<th>Cardiovascular System</th>
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</thead>
<tbody>
<tr>
<td>The <strong>aorta</strong> (main blood vessel that carries blood from the heart) may be enlarged and weakened.</td>
</tr>
<tr>
<td>The layers of the aorta may be separated, causing it to tear more easily.</td>
</tr>
<tr>
<td>The mitral valve that separates the upper and lower halves of the left side of the heart may be enlarged and may not work properly.</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Skeletal System</th>
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</thead>
<tbody>
<tr>
<td>Tall and thin body type</td>
</tr>
<tr>
<td><strong>Scoliosis</strong> (curvature of the spine)</td>
</tr>
<tr>
<td>Chest sinks in or sticks out</td>
</tr>
<tr>
<td>Flexible joints</td>
</tr>
<tr>
<td>Flat feet</td>
</tr>
<tr>
<td>Teeth very crowded together</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Ocular System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe <strong>myopia</strong> (nearsightedness)</td>
</tr>
<tr>
<td>Dislocated eye lens</td>
</tr>
<tr>
<td>Detached retina</td>
</tr>
<tr>
<td>Early glaucoma or cataracts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Body Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stretch marks on skin, not from pregnancy or weight gain</td>
</tr>
<tr>
<td>Sudden lung collapse</td>
</tr>
<tr>
<td>Swelling of the sac that surrounds the spinal column</td>
</tr>
</tbody>
</table>
To make a diagnosis of Marfan syndrome, the doctor compares the patient’s medical history, results of a physical examination, and results from laboratory tests with the set of diagnostic criteria. If no one in the patient’s family has Marfan syndrome, the doctor makes the diagnosis if the patient has major criteria in two different body systems and minor criteria in a third body system. If the patient has a parent or sibling with Marfan syndrome, the doctor makes the diagnosis if the patient has major criteria in one body system and minor criteria in a second body system. A person may have many features associated with Marfan syndrome in a single body system but still not be diagnosed with the disorder.

**Treatment of Marfan Syndrome:** Although there’s no cure for Marfan syndrome, certain treatments can minimize or, in some cases, prevent complications. Depending on which body systems are affected, an appropriate team of specialists create an individualized treatment program. Table 11 lists some of the available disease-management options.

### 5.3 Childhood Leukemia

Leukemias are cancers of the blood or bone marrow that usually result in the overproduction of **white blood cells** and that are classified by how long it takes for the disease to appear and worsen (acute and chronic) and by the type of blood cell affected (lymphocytic or myeloid):

- **Acute leukemia** is characterized by the rapid appearance of immature blood cells, called blasts, produced in the bone marrow. This overcrowding of cells prevents the bone marrow from making healthy blood cells. The lack of healthy white blood cells (which help fight infection) leaves the patient vulnerable to repeated bouts of colds and flu. The lack of healthy **red blood cells** leads to anemia and fatigue. Acute forms of leukemia may occur in people of all ages, but they are often the forms seen in children.

- **Chronic leukemia** is characterized by a more gradual accumulation of relatively mature blood cells. It may take months or years to progress. This form of leukemia can also be found in people of all ages but is more common among older people.

- **Lymphocytic leukemia** is a cancer of the B cells, a kind of lymphocyte (or white blood cell) that plays a role in the immune system.

- **Myeloid leukemia** is a cancer of other cells, such as red blood cells, **platelets**, and other types of white blood cells.

This supplement is concerned with **acute lymphoblastic leukemia (ALL)**, which is the most common form of leukemia in children. The Leukemia and Lymphoma Society estimates that in 2009, there were 5,760 new cases of ALL in children in the United States.

**Symptoms of ALL:** The most common symptoms appearing in children with ALL are fever; recurring infections; easy bruising or bleeding; lumps in the neck, underarms, stomach, or groin; pain or a feeling of fullness below the ribs; fatigue; and the loss of appetite.
Diagnosis of ALL: In addition to a physical exam and patient history, blood tests are used to diagnose ALL. The different types of blood cells are counted to determine whether they are present in abnormal ratios. A biopsy of the bone marrow allows cells from the bone, blood, and bone marrow to be examined for an abnormal appearance. A cytogenetic analysis also may be carried out, because some forms of ALL are associated with the appearance of trisomies (having three instead of the normal two copies of a chromosome) in the affected cells. Trisomies can be detected in a kind of photograph of the chromosomes called a karyotype. To make the karyotype easier to analyze, the individual chromosomes are cut out from the original photograph and rearranged in pairs. A trisomy involving one or more chromosomes may be seen in the leukemia cells but not in unaffected cells taken from other parts of the body.

Treatment of ALL: The treatment of ALL has made continual progress since the 1960s, mostly thanks to the results of clinical trials on children with the disease. During clinical trials, one group of children receives the so-called standard treatment, which is the best care known at the time. Researchers compare the health of this group of children with one or more additional groups of children who receive a modified form of the standard care that is designed to test some new treatment, such as a different dose or a new drug. The success of a treatment is described in terms of its five-year survival rate, which refers to the percentage of patients who live at least five years after cancer was diagnosed. Today, the five-year survival rate for children with ALL in the United States is over 80 percent (American Cancer Society, 2009).

Current treatment for ALL consists of several phases:
- **Induction Chemotherapy**: This initial phase uses a combination of drugs such as prednisone and vincristine to kill most of the cancer cells.
- **Consolidation Therapy**: In this phase, a different combination of drugs is used to target any remaining cancer cells.
- **Preventive Therapy**: The aim of this phase is to prevent the spread of the disease to the central nervous system. It may involve irradiation of the head and the injection of drugs directly into the spine.
- **Maintenance Therapy**: In this final phase of treatment, lower doses of the drugs are administered for up to three years in an attempt to keep the disease from reappearing.

Some high-risk ALL patients may also receive a bone marrow transplant.

Causes of ALL: ALL has no single cause. Ultimately, ALL is a genetic disease in the sense that it results from genetic damage (mutation)
to a single cell that then spreads to progeny cells. The DNA damage may result from natural or medical radiation (that is, from the sun or medical X-rays) or from environmental exposure to toxic substances such as the solvent benzene. ALL is sometimes linked to infection, as from the human T-lymphotropic virus. Most cases of ALL are spontaneous, meaning that the mutations occurred spontaneously in that individual patient and were not inherited. ALL can, however, sometimes run in families.

6.0 Rare Diseases as a Topic for the Middle School Science Classroom

The topic of rare diseases provides an excellent context for teaching core life science content in the middle school classroom (see Tables 3 and 4). According to the National Science Education Standards (NSES), middle school students should develop a basic understanding of heredity and genetics (NRC, 1996). Since the majority of rare diseases have a genetic basis, we can use them as real-life examples of the relationship between genes and health. Many rare diseases are linked to single genes, making them appropriate for study by middle school students who have only basic knowledge of the relationship between genotype and phenotype. In addition, single-gene disorders allow for the study of the fundamentals of inheritance.

Middle school students are often introduced to the concept of disease as the breakdown of structures or functions of an organism. Rare diseases offer opportunities to expand on that concept by exploring how diseases are linked, not just to genetics, but also to the environment and infection by pathogens. Infectious diseases are an important example of an interrelationship between organisms, since we can use them to illustrate structural similarities and differences between the cells of the host and the pathogen. Furthermore, students can examine the structure-function relationship of systems in the body by studying the differences between diseased and unaffected states.

Rare diseases offer an engaging context for exploring body systems, which are often treated as a vocabulary-laden series of diagrams.

Figure 7. A karyotype from a leukemia patient may show abnormal numbers of chromosomes.

Source: Genetics Department, Affiliated Laboratories, Inc., Bangor, Maine
Investigating how a rare disease affects a body system can help students understand how that system normally works. The wide variety of rare diseases ensures that we can select examples that focus primarily on individual body systems. We can use other rare diseases to illustrate functional interactions between body systems.

Furthermore, this curriculum supplement gives students a chance to address any misconceptions they may have about rare diseases. Most students know very little about rare diseases. They usually haven't experienced one themselves or in their immediate family. This lack of familiarity can promote misconceptions about rare diseases and the healthcare system's responses to them. An informal survey of Web sites for support groups for patients with rare diseases suggests several misconceptions that the curriculum supplement should address, including the following:

- **All Rare Diseases Are Being Actively Researched:** Many people, especially those with health insurance and good health, may not be aware of the limitations of the healthcare system in terms of the resources available to treat patients and the state of medical knowledge available to develop drugs and treatments for rare diseases. Despite the efforts of the government, pharmaceutical companies, and patient support organizations, many rare diseases are underfunded and not actively researched.

- **A Disease Must Not Be Rare If It Is Well Known:** Students often assume that if they have heard of a disease, it must not be rare. Examples of well-known rare diseases are cystic fibrosis, sickle cell anemia, and mumps. By addressing this misconception, this curriculum supplement can help students understand the statistical definition of rare diseases.

- **Very Little Is Known about Rare Diseases:** Although limited research has been done on some rare diseases, others have been researched extensively. Especially after the passage of the Orphan Drug Act in 1983, increased funds from the U.S. government have been available to study rare diseases.

- **Family Doctors Are Well Equipped to Diagnose Rare Diseases:** Despite technologies such as the Internet that make information about rare diseases available at a moment's notice, most family doctors are ill equipped to diagnose a rare disease. In many instances, a patient with a rare disease will be the first one ever encountered by the doctor. Furthermore, many rare diseases share symptoms with more-common diseases, and doctors naturally think of common diseases first when considering the diagnosis. This knowledge may help students understand why many patients with rare diseases will visit a number of different doctors over a one-to-five-year period before obtaining a correct diagnosis.

- **Rare Diseases Are Fatal:** Since, by definition, most people have not encountered rare diseases firsthand, their impressions about these diseases come from print and television media. Stories about patients with rare diseases tend to emphasize children and gravely ill people. Rare diseases display the same variations as more-common diseases. Some rare diseases are, in fact, fatal and strike their victims during childhood. Others are less serious and can be cured or effectively managed.
7.0 Scientific Inquiry
Scientific inquiry refers to the diverse ways in which scientists study the natural world and propose explanations based on the evidence derived from their work. Inquiry also refers to the activities of students in which they develop knowledge and understanding of scientific ideas, as well as an understanding of how scientists study the natural world.
—NRC, 1996

7.1 Scientific Inquiry as a Topic for the Middle School Science Classroom
Scientific inquiry is a topic well suited to the middle school classroom. The NSES stress both abilities and understandings about inquiry (NRC, 1996; see Section 7.2 in Inquiry in the National Science Education Standards (NRC, 2000)). As discussed in the NSES, students are naturally curious about the world. Inquiry-based instruction offers an opportunity to
• engage student interest in and knowledge about scientific investigation,
• sharpen critical-thinking skills,
• distinguish science from nonscience,
• make students aware of the importance of basic research, and
• humanize the image of scientists.

7.2 Scientific Inquiry in the National Science Education Standards
Inquiry is a multifaceted activity that involves making observations; posing questions; examining books and other sources of information to see what is already known; planning investigations; reviewing what is already known in light of experimental evidence; using tools to gather, analyze, and interpret data; proposing answers, explanations, and predictions; and communicating the results. Inquiry requires identification of assumptions, use of critical and logical thinking, and consideration of alternative explanations.
—NRC, 1996

The National Science Education Standards recognize inquiry as both a learning goal and a teaching method (NRC, 1996). To that end, the content standards for scientific inquiry include both abilities and understandings about inquiry. The NSES identify five essential elements of inquiry teaching and learning that apply across all grade levels:
1. Learners are engaged by scientifically oriented questions.
   Strategies to improve students’ ability to ask scientific questions include providing examples and modeling the formation of testable questions (Krajcik et al., 1998), providing materials that stimulate questions (Chin and Brown, 2002; Harlen, 2001), and encouraging students to formulate their own questions (Harlen, 2001).
2. Learners give priority to evidence, which allows them to develop and evaluate explanations that address scientifically oriented questions.
   Scientists obtain evidence in the form of scientific data by recording observations and making measurements. They can check the accuracy of the data by repeating the observations or making new measurements. In the classroom, students use such data to construct explanations for scientific phenomena. Unfortunately, students have difficulty both using appropriate evidence (Sandoval and Reiser, 1997) and including it in their written explanations (Bell and Linn, 2000).

Figure 9. In the classroom, scientific inquiry can be both a learning goal and a teaching method.
3. Learners formulate explanations from evidence to address scientifically oriented questions. Scientific explanations are consistent with the available evidence and are subject to criticism and revision. Furthermore, scientific explanations extend beyond current knowledge and propose new understandings that extend the knowledge base. The same is true for students who generate new ideas by building on their personal knowledge base. Explanations are rarely a part of classroom practice, and students need to be explicitly taught how to formulate scientific explanations (Kuhn et al., 2006; McNeill and Krajcik, 2007).

4. Learners evaluate their explanations in light of alternative explanations, particularly those reflecting scientific understanding. Scientific inquiry differs from other forms of inquiry in that proposed explanations may be revised or thrown out altogether in light of new information. As students compare their results with those of others, they may consider alternative explanations.

5. Learners communicate and justify their proposed explanations. Scientists communicate their results in such detail that other scientists can reproduce their work. This gives science an important quality-control mechanism. Other scientists can use the results to investigate new but related questions. Students also benefit by sharing their results with their classmates. This gives them a chance to ask questions, examine evidence, identify faulty reasoning, consider whether conclusions go beyond the data, and suggest alternative explanations.

The following chart (Table 12) lists the abilities and understandings about inquiry appropriate for middle school, taken from the NSES content standards for scientific inquiry (NRC, 1996). These abilities and understandings are consistent with student performance expectations in the National Assessment of Educational Progress (NCES, 2011).

Table 12. NSES Content Standards for Scientific Inquiry, Grades 5–8

<table>
<thead>
<tr>
<th>Fundamental Abilities Necessary to Do Scientific Inquiry</th>
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<tbody>
<tr>
<td>• Identify questions that can be answered through scientific investigations.</td>
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<td>• Design and conduct a scientific investigation.</td>
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<tr>
<td>• Use appropriate tools and techniques to gather, analyze, and interpret data.</td>
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<td>• Develop descriptions, explanations, predictions, and models using evidence.</td>
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<td>• Think critically and logically to make the relationships between evidence and explanations.</td>
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<td>• Recognize and analyze alternative explanations and predictions.</td>
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<tr>
<td>• Communicate scientific procedures and explanations.</td>
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<tr>
<td>• Use mathematics in all aspects of scientific inquiry.</td>
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<tr>
<th>Fundamental Understandings about Scientific Inquiry</th>
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<tr>
<td>• Different kinds of questions suggest different kinds of scientific investigations.</td>
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<tr>
<td>• Current scientific knowledge and understanding guide scientific investigations.</td>
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<td>• Mathematics is important in all aspects of scientific inquiry.</td>
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<tr>
<td>• Technology used to gather data enhances accuracy and allows scientists to analyze and quantify results of investigations.</td>
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<tr>
<td>• Scientific explanations emphasize evidence, have logically consistent arguments, and use scientific principles, models, and theories.</td>
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<tr>
<td>• Science advances through legitimate skepticism.</td>
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<tr>
<td>• Scientific investigations sometimes result in new ideas and phenomena for study, generate new methods or procedures for an investigation, or develop new technologies to improve the collection of data.</td>
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