Human Genetic Variation

under a contract from the
National Institutes of Health

National Human Genome Research Institute

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Contents

Foreword

This curriculum supplement brings into the classroom new information about some of the exciting medical discoveries being made at the National Institutes of Health (NIH) and their effects on public health. This set is being distributed to teachers around the country free of charge by the NIH to improve science literacy and to foster student interest in science. These tools may be copied for classroom use, but may not be sold.

This set was developed at the request of NIH Director Harold Varmus, M.D., as part of a major new initiative to create a curriculum supplement series (for grades kindergarten through 12) that complies with the *National Science Education Standards*.[1] This set is part of a continuing series being developed by the NIH Office of Science Education (OSE) in cooperation with NIH institutes with wide-ranging medical and scientific expertise. Three new supplements are planned per year.

The curriculum supplements use up-to-date, accurate scientific data and case studies (not contrived). The supplements contain extensive background information for teachers and

- use creative, inquiry-based activities to promote active learning and stimulate student interest in medical topics;
- deepen students' understanding of the importance of basic research to advances in medicine and health;
- offer students an opportunity to apply creative and critical thinking;
- foster student analysis of the direct and indirect effects of scientific discoveries on their individual lives and on public health; and
- encourage students to take more responsibility for their own health.

Each supplement contains several activities that may be used in sequence or as individual activities designed to fit into 45 minutes of classroom time. The printed materials may be used in isolation or in conjunction with the CD-ROMs, which offer scenarios, simulations, animations, and videos.

The first three supplements in the series (listed below) are designed for use in senior high school science classrooms:

- *Emerging and Re-emerging Infectious Diseases* (with expertise from the National Institute of Allergy and Infectious Diseases)
- *Cell Biology and Cancer* (with expertise from the National Cancer Institute)
- *Human Genetic Variation* (with expertise from the National Human Genome Research Institute)

We appreciate the invaluable contributions of the talented staff at Biological Sciences Curriculum Study (BSCS) and Videodiscovery, Inc., who developed these materials. We are also grateful to the scientific advisers at the NIH institutes who worked long and hard on this project. Finally, we thank the teachers and students across the country who participated in focus groups and field tests to help ensure that these materials are both engaging and effective.

We are eager to know about your particular experience with the supplements. Your comments help this program to evolve and grow. For continuing updates on the curriculum supplement series or to make comments, please visit
http://science-education.nih.gov/supplements.
You may also send your suggestions to

Curriculum Supplement Series
Office of Science Education
National Institutes of Health
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Bethesda, MD 20892

I hope you find our series a valuable addition to your classroom and wish you a productive school year.

Bruce A. Fuchs, Ph.D.
Director
Office of Science Education
National Institutes of Health

1 The National Academy of Sciences released the *National Science Education Standards* in December 1995 to outline what all citizens should understand about science by the time they graduate from high school. The *Standards* encourage teachers to select major science concepts or themes that empower students to use information to solve problems rather than to stress memorization of large volumes of unconnected bits of information.

About the National Institutes of Health ⟆

The National Institutes of Health (NIH)—the world's top medical research center—is charged with addressing the health concerns of the nation. The NIH is the largest U.S. governmental sponsor of health studies conducted nationwide.

Simply described, the NIH's goal is to acquire new knowledge to help prevent, detect, diagnose, and treat disease and disability, from the rarest genetic disorder to the common cold. The NIH works toward that goal by conducting research in its own laboratories in Bethesda, Maryland; supporting the research of nonfederal scientists throughout the country and abroad; helping to train research investigators; and fostering communication of medical information to the public.

The NIH Supports Research

A principal concern of the NIH is to invest wisely the tax dollars entrusted to it for the support and conduct of medical research. Approximately 82 percent of the investment is made through grants and contracts supporting research and training in more than 2,000 universities, medical schools, hospitals, and research institutions throughout the United States and abroad.

Approximately 10 percent of the budget goes to more than 2,000 projects conducted mainly in NIH laboratories. About 80 percent covers support costs of research conducted both within and outside the NIH.

NIH Research Grants

To apply for a research grant, an individual scientist must submit an idea in a written application. Each application undergoes a peer review process. A panel of scientific experts, who are active researchers in the medical sciences, first evaluates the scientific merit of the application. Then, a national advisory council or board, comprised of eminent scientists as well as public members who are interested in health issues or the medical sciences, determines the project's overall merit and priority. Because funds are limited, the process is very competitive.

The Nobelists

The rosters of those who have conducted research, or who have received NIH support over the years, include some of the world's most illustrious scientists and physicians. Among them are 97 scientists who have won Nobel Prizes for achievements as diverse as deciphering the genetic code and learning what causes hepatitis.

Five Nobelists made their prize-winning discoveries in NIH laboratories: Doctors Christian B. Anfinsen, Julius Axelrod, D. Carleton Gajdusek, Marshall W. Nirenberg, and Martin Rodbell.

Impact of the NIH on the Nation's Health

The research programs of the NIH have been remarkably successful during the past 50 years. NIH-funded scientists have made substantial progress in understanding the basic mechanisms of disease and have vastly improved the preventive, diagnostic, and therapeutic options available.

During the last few decades, NIH research played a major role in making possible achievements like these:

- Mortality from heart disease, the number one killer in the United States, dropped by 36 percent between 1977 and 1999.
- Improved treatments and detection methods increased the relative five-year survival rate for people with cancer to 60 percent.
- Those suffering from depression now look forward to returning to work and leisure activities, thanks to treatments that give them an 80 percent chance to resume a full life in a matter of weeks.
- Vaccines protect against infectious diseases that once killed and disabled millions of children and adults.
- In 1990, NIH researchers performed the first trial of gene therapy in humans. Scientists are increasingly able to locate, identify, and describe the functions of many of the genes in the human genome. The ultimate goal is to develop screening tools and gene therapies for the general population for cancer and many other diseases.

Educational and Training Opportunities at the NIH

The NIH offers a myriad of opportunities including summer research positions for students. For details, visit http://science-education.nih.gov/students.

For more information about the NIH, visit http://www.nih.gov.

The NIH Office of Science Education

The NIH Office of Science Education (OSE) is bringing exciting new resources free of charge to science teachers of grades kindergarten through 12. OSE learning tools support teachers in training the next generation of scientists and scientifically literate citizens. These materials cover information not available in standard textbooks and allow students to explore biological concepts using real world examples. In addition to the curriculum supplement, OSE provides a host of valuable resources accessible through the OSE Web site (http://science-education.nih.gov), such as:

- **Snapshots of Science and Medicine**.[2] This online magazine—plus interactive learning tools—is designed for ease of use in high school science classrooms. Three issues, available for free, are published during the school year. Each focuses on a new area of research and includes four professionally written articles on findings, historical background, related ethical questions, and profiles of people working in the field. Also included are a teaching guide, classroom activities, handouts, and more. (http://science-education.nih.gov/snapshots)
- **Women Are Scientists Video and Poster Series**.[3] This series provides teachers and guidance counselors with free tools to encourage young women to pursue careers in the medical field. The informative, full-color video and poster sets focus on some of the careers in which women are currently underrepresented. The first set, titled "Women are Surgeons," has been completed. The second, "Women are Pathologists," will be finished in 2000, and the third, "Women are Researchers," in 2001. (http://science-education.nih.gov/women)
- **Internship Programs**. Visit the OSE Web site to obtain information on a variety of NIH programs open to teachers and students. (http://science-education.nih.gov/students)
- **National Science Teacher Conferences**. Thousands of copies of NIH materials are distributed to teachers for free at the OSE exhibit booth at conferences of the National Science Teachers Association and the National Association of Biology Teachers. OSE also offers teacher-training workshops at many conferences. (http://science-education.nih.gov/exhibits)

In the development of learning tools, OSE supports science education reform as outlined in the *National Science Education Standards* and related guidelines.

We welcome your comments about existing resources and suggestions about how we may best meet your needs. Feel free to send your comments to us at http://science-education.nih.gov/feedback.

2, 3 These projects are collaborative efforts between OSE and NIH Office of Research on Women's Health.

About the National Human Genome Research Institute

The National Human Genome Research Institute (NHGRI) is leading the international effort to identify and characterize the estimated 80,000 to 100,000 genes that orchestrate a single cell's development into a human infant and then an adult, and that govern whether that individual will be susceptible to diseases such as muscular dystrophy, cancer, Alzheimer disease, high blood pressure, and obesity.

Part of the National Institutes of Health, the federal government's biomedical research arm, NHGRI has set the year 2003 as its deadline for completing the DNA sequence of the human genome, our genetic blueprint.

Completing the sequence of the human genome and deciphering its functions are the first step toward "molecular medicine," the revolutionary approach to diagnosis and treatment that will create targeted, individualized health care in the early 21st century. Then, each person should be able to determine his or her risk for disease through genetic tests. If the tests indicate increased susceptibility to a disease, the individual will be able to obtain counseling on how to reduce that risk—perhaps by periodic medical check-ups, a special diet and other lifestyle changes, as well as drugs tailored to his or her genetic profile. Treatment of disease also likely will include gene therapies to replace, compensate for, or repair the genes that play a role in the disease.

In addition to genetics research, NHGRI sponsors research exploring the potential ethical, legal, and social consequences of the anticipated genetics revolution in medicine. By focusing now on preventing the potential misuses of genetic information in insurance and employment, NHGRI is helping ensure that genetic information will be used as it was intended: to promote human health and save lives.

For more information about the National Human Genome Research Institute, visit its Web site at: http://www.nhgri.nih.gov.

Introduction to the Module

Human Genetic Variation has two central objectives. The first is to introduce students to major concepts related to human genetic variation. *Homo sapiens* comprises a single species, yet the more than 6 billion of us alive today, and the millions who preceded us following the emergence of fully modern humans some 150,000 years ago, are a diverse lot. One look at the students who sit in your class each day is all you need to confirm that fact. The module's first objective is to help students recognize and understand this variation.

The second objective is to convey to students the relationship between basic biomedical research and the improvement of personal and public health. The new knowledge that scientists are gaining as they map and sequence the human genome is rapidly changing the practice of medicine, and it is vital that citizens recognize these changes and are prepared to deal with them. Being prepared involves understanding the basic science that underlies new medical practices and therapies, and recognizing the complex issues and questions that some of these procedures and therapies raise. Thus, the module's second objective is to help students think about how the detailed analysis of human genetic variation is already changing their lives.

Figure 1 Humans are a genetically diverse lot. How will understanding this diversity at a molecular level change our lives?

If recognizing human variation is common, it is not new; certainly our ancestors realized that no two humans are identical. Nevertheless, biologists before Charles Darwin subscribed to what Ernst Mayr has called "essentialist thinking": the notion that each species is defined by an invariant type that limits the ability of its members to vary too much from the essential nature of the species. Among Darwin's great insights was the recognition that the essentialist view is incorrect, that the members of any given species are highly variable, and that some variations within a species will confer selective advantage on those individuals that possess them. This variation within species makes differential selection, and therefore evolution, possible. Mayr has called this view "population thinking," and it pervades modern biology.

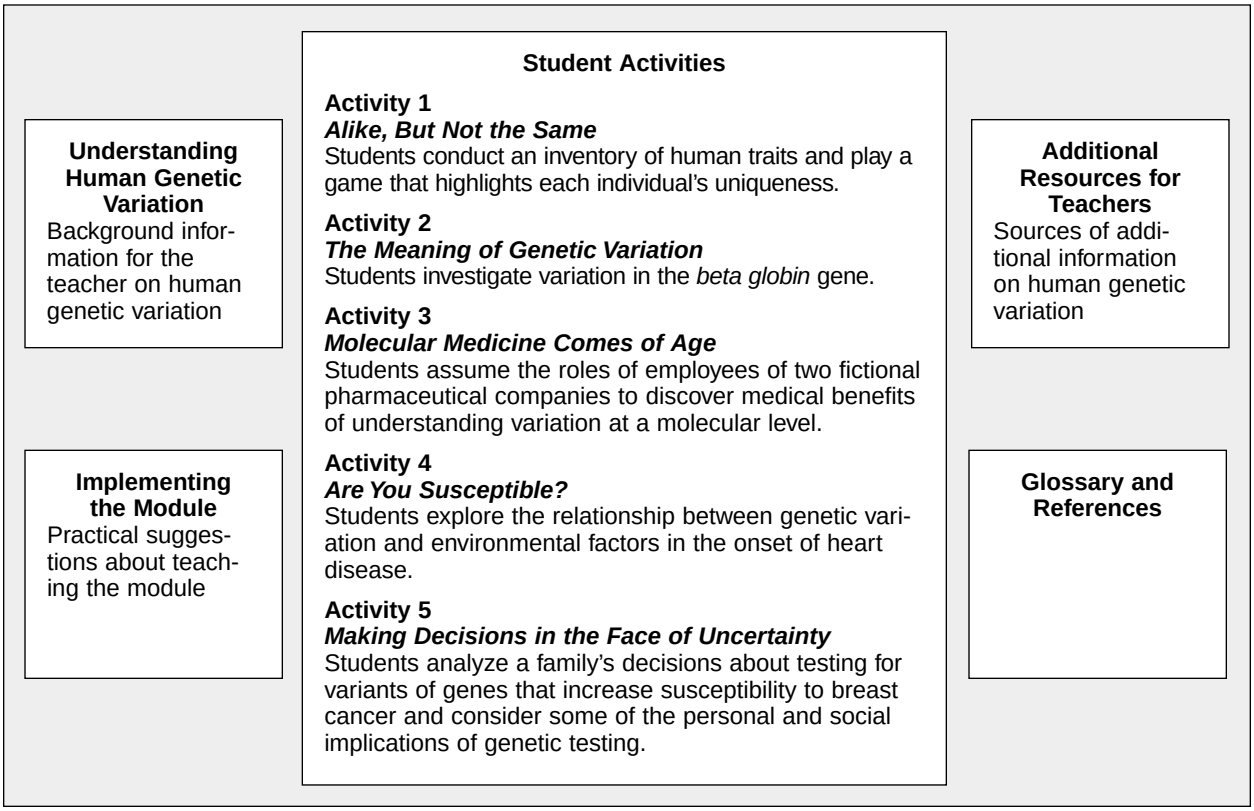
Darwin, however, even while working as Mendel's contemporary, was confounded by his inability to identify the root source of biological variation or the mechanisms by which those variations are transmitted to subsequent generations of organisms within the same species. The rediscovery of Mendel's work in the early 1900s provided those answers, and the reconciliation of Mendelism and Darwinism in the modern synthesis of evolution in the 1930s and 1940s formed the basis for the biology we practice and teach today.

The identification of DNA as the genetic material in the early 1940s, and the elucidation of its structure about a decade later, opened the way for an analysis of genetic variation at the molecular level. That analysis proceeds at breakneck speed today, propelled by a host of powerful new techniques in molecular biology.

This module focuses on our progress in analyzing human genetic variation and the impact of that analysis on individuals and society. There are many concepts we could have addressed, but we have chosen, with the help of a variety of experts in this field, a relatively small number for exploration by your students. Those concepts follow.

- Humans share many basic characteristics, but there is a wide range of variation in human traits. Most human traits are multifactorial: They are influenced by multiple genes and environmental factors.
- The ultimate source of genetic variation is differences in DNA sequences. Most of those genetic differences do not affect how individuals function. Some genetic variation, however, is associated with disease, and some improves the ability of the species to survive changes in the environment. Genetic variation, therefore, is the basis for evolution by natural selection.
- One of the benefits of understanding human genetic variation at a molecular level is its practical value for helping us understand and treat disease. The development of effective gene-based therapies is an exciting outcome of human genetic research. These therapies, however, are potentially many years away for many diseases.
- Studying the genetic and environmental factors involved in multifactorial diseases will lead to increased diagnosis, prevention, and treatment of disease.
- Our growing understanding of human genetic variation will allow us to identify genes that are

Figure 2 This diagram identifies the module's major sections and describes their contents.



associated with common diseases such as cancer. Genetic testing to identify individuals who have variations that make them susceptible to certain diseases can help people make decisions in uncertain circumstances and holds the prospect for more effective prevention and treatment. However, this capability also raises difficult questions about the uses of genetic information, questions that illustrate the personal and social implications of biological research.

We hope the five activities provided in this module (Figure 2) will be effective vehicles to carry these concepts to your students. Although the activities contain much interesting information about various aspects of human genetics, we suggest that you focus your students' attention on the major concepts the module was designed to convey. The concluding steps in each activity are intended to focus the students' attention on those concepts as the activity draws to a close.

Understanding Human Genetic Variation

Genetics is the scientific study of inherited variation. **Human genetics**, then, is the scientific study of inherited human variation.

Why study human genetics? One reason is simply an interest in better understanding ourselves. As a branch of genetics, human genetics concerns itself with what most of us consider to be the most interesting species on earth: *Homo sapiens*. But our interest in human genetics does not stop at the boundaries of the species, for what we learn about human genetic variation and its sources and transmission inevitably contributes to our understanding of genetics in general, just as the study of variation in other species informs our understanding of our own.

A second reason for studying human genetics is its practical value for human welfare. In this sense, human genetics is more an applied science than a fundamental science. One benefit of studying human genetic variation is the discovery and description of the genetic contribution to many human diseases. This is an increasingly powerful motivation in light of our growing understanding of the contribution that genes make to the development of diseases such as cancer, heart disease, and diabetes. In fact, society has been willing in the past and continues to be willing to pay significant amounts of money for research in this area, primarily because of its perception that such study has enormous potential to improve human health. This perception, and its realization in the discoveries of the past 20 years, have led to a marked increase in the number of people and organizations involved in human genetics.

This second reason for studying human genetics is related to the first. The desire to develop medical practices that can alleviate the suffering associated with human disease has provided strong support to basic research. Many basic biological phenomena have been discovered and described during the course of investigations into particular disease conditions. A classic example is the knowledge about human sex chromosomes that was gained through the study of patients with sex chromosome abnormalities. A more current example is our rapidly increasing understanding of the mechanisms that regulate cell growth and reproduction, understanding that we have gained primarily through a study of genes that, when mutated, increase the risk of cancer.

Likewise, the results of basic research inform and stimulate research into human disease. For example, the development of recombinant DNA techniques

Figure 3 Recombinant techniques have transformed the study of human genetics.

(Figure 3) rapidly transformed the study of human genetics, ultimately allowing scientists to study the detailed structure and functions of individual human genes, as well as to manipulate these genes in a variety of previously unimaginable ways.

A third reason for studying human genetics is that it gives us a powerful tool for understanding and describing human evolution. At one time, data from physical anthropology (including information about skin color, body build, and facial traits) were the only source of information available to scholars interested in tracing human evolutionary history. Today, however, researchers have a wealth of genetic data, including molecular data, to call upon in their work.

How Do Scientists Study Human Genetic Variation?

Two research approaches were historically important in helping investigators understand the biological basis of heredity. The first of these approaches, transmission genetics, involved crossing organisms and studying the offsprings' traits to develop hypotheses about the mechanisms of inheritance. This work demonstrated that in some organisms at least, heredity seems to follow a few definite and rather simple rules.

The second approach involved using cytologic techniques to study the machinery and processes of cellular reproduction. This approach laid a solid foundation for the more conceptual understanding of inheritance that developed as a result of transmission genetics. By the early 1900s, cytologists had demonstrated that heredity is the consequence of the genetic continuity of cells by cell division, had identified the gametes as the vehicles that transmit genetic information from one generation to another, and had collected strong evidence for the central role of the nucleus and the chromosomes in heredity.

As important as they were, the techniques of transmission genetics and cytology were not enough to help scientists understand human genetic variation at the level of detail that is now possible. The central advantage that today's molecular techniques offer is that they allow researchers to study DNA directly. Before the development of these techniques, scientists studying human genetic variation were forced to make inferences about molecular differences from the phenotypes produced by mutant genes. Furthermore, because the genes associated with most single-gene disorders are relatively rare, they could be studied in only a small number of families. Many of the traits associated with these genes also are recessive and so could not be detected in people with heterozygous genotypes. Unlike researchers working with other species, human geneticists are restricted by ethical considerations from performing experimental, "at-will" crosses on human subjects. In addition, human generations are on the order of 20 to 40 years, much too slow to be useful in classic breeding experiments. All of these limitations made identifying and studying genes in humans both tedious and slow.

In the last 50 years, however, beginning with the discovery of the structure of DNA and accelerating significantly with the development of recombinant DNA techniques in the mid-1970s, a growing battery of molecular techniques has made direct study of human DNA a reality. Key among these techniques are restriction analysis and molecular recombination, which allow researchers to cut and rejoin DNA molecules in highly specific and predictable ways; amplification techniques, such as the polymerase chain reaction (PCR), which make it possible to make unlimited copies of any fragment of DNA; hybridization techniques, such as fluorescence in situ hybridization, which allow scientists to compare DNA samples from different sources and to locate specific base sequences within samples; and the automated sequencing techniques that today are allowing workers to sequence the human genome at an unprecedented rate.

On the immediate horizon are even more powerful techniques, techniques that scientists expect will have a formidable impact on the future of both research and clinical genetics. One such technique, **DNA chip technology** (also called DNA microarray technology), is a revolutionary new tool designed to identify mutations in genes or survey expression of tens of thousands of genes in one experiment.

In one application of this technology, the chip is designed to detect mutations in a particular gene. The DNA microchip consists of a small glass plate encased in plastic. It is manufactured using a process similar to the process used to make computer microchips. On its surface, it contains synthetic single-stranded DNA sequences identical to that of the normal gene and all possible mutations of that gene. To determine whether an individual possesses a mutation in the gene, a scientist first obtains a sample of DNA from the person's blood, as well as a sample of DNA that does not contain a mutation in that gene. After denaturing, or separating, the DNA samples into single strands and cutting them into smaller, more manageable fragments, the scientist labels the fragments with fluorescent dyes: the person's DNA with red dye and the normal DNA with green dye. Both sets of labeled DNA are allowed to hybridize, or bind, to the synthetic DNA on the chip. If the person does not have a mutation in the gene, both DNA samples will hybridize equivalently to the chip and the chip will appear uniformly yellow. However, if the person does possess a mutation, the mutant sequence on the chip will hybridize to the patient's sample, but not to the normal DNA, causing it (the chip) to appear red in that area. The scientist can then examine this area more closely to confirm that a mutation is present.

DNA microarray technology is also allowing scientists to investigate the activity in different cell types of thousands of genes at the same time, an advance that will help researchers determine the complex functional relationships that exist between individual genes. This type of analysis involves placing small snippets of DNA from hundreds or thousands of genes on a single microscope slide, then allowing fluorescently labeled mRNA molecules from a particular cell type to hybridize to them. By measuring the fluorescence of each spot on the slide, scientists can determine how active various genes are in that cell type. Strong fluorescence indicates that many mRNA molecules hybridized to the gene and, therefore, that the gene is very active in that cell type. Conversely, no fluorescence indicates that none of the cell's mRNA molecules hybridized to the gene and that the gene is inactive in that cell type.

Although these technologies are still relatively new and are being used primarily for research, scientists expect that one day they will have significant clinical applications. For example, DNA chip technology has the potential to significantly reduce the time and expense involved in genetic testing. This technology or others like it may one day help make it possible to define an individual's risk of developing many types of hereditary cancer as well as other common disorders, such as heart disease and diabetes. Likewise, scientists may one day be able to classify human cancers based on the patterns of gene activity in the tumor cells and then be able to design treatment strategies that are targeted directly to each specific type of cancer.

How Much Genetic Variation Exists Among Humans?

Homo sapiens is a relatively young species and has not had as much time to accumulate genetic variation as have the vast majority of species on earth, most of which predate humans by enormous expanses of time. Nonetheless, there is considerable genetic variation in our species. The human genome comprises about 3×10^9 base pairs of DNA, and the extent of human genetic variation is such that no two humans, save identical twins, ever have been or will be genetically identical. Between any two humans, the amount of genetic variation—biochemical individuality—is about .1 percent. This means that about one base pair out of every 1,000 will be different between any two individuals. Any two (diploid) people have about 6×10^6 base pairs that are different, an important reason for the development of automated procedures to analyze genetic variation.

The most common **polymorphisms** (or genetic differences) in the human genome are single base-pair differences. Scientists call these differences SNPs, for single-nucleotide polymorphisms. When two different haploid genomes are compared, SNPs occur, on average, about every 1,000 bases. Other types of polymorphisms—for example, differences in copy number, insertions, deletions, duplications, and rearrangements—also occur, but much less frequently.

Notwithstanding the genetic differences between individuals, all humans have a great deal of their

genetic information in common. These similarities help define us as a species. Furthermore, genetic variation around the world is distributed in a rather continuous manner; there are no sharp, discontinuous boundaries between human population groups. In fact, research results consistently demonstrate that about 85 percent of all human genetic variation exists *within* human populations, whereas about only 15 percent of variation exists *between* populations (Figure 4). That is, research reveals that *Homo sapiens* is one continuously variable, interbreeding species. Ongoing investigation of human genetic variation has even led biologists and physical anthropologists to rethink traditional notions of human racial groups. The amount of genetic variation between these traditional classifications actually falls below the level that taxonomists use to designate subspecies, the taxonomic category for other species that corresponds to the designation of race in *Homo sapiens*. This finding has caused some biologists to call the validity of race as a biological construct into serious question.

Analysis of human genetic variation also confirms that humans share much of their genetic information with the rest of the natural world—an indication of the relatedness of all life by descent with modification from common ancestors. The highly conserved nature of many genetic regions across considerable evolutionary distance is especially obvious in genes related to development. For example, mutations in the *patched* gene produce developmental abnormalities in *Drosophila*, and mutations in the *patched* homolog in humans produce analogous structural deformities in the developing human embryo.

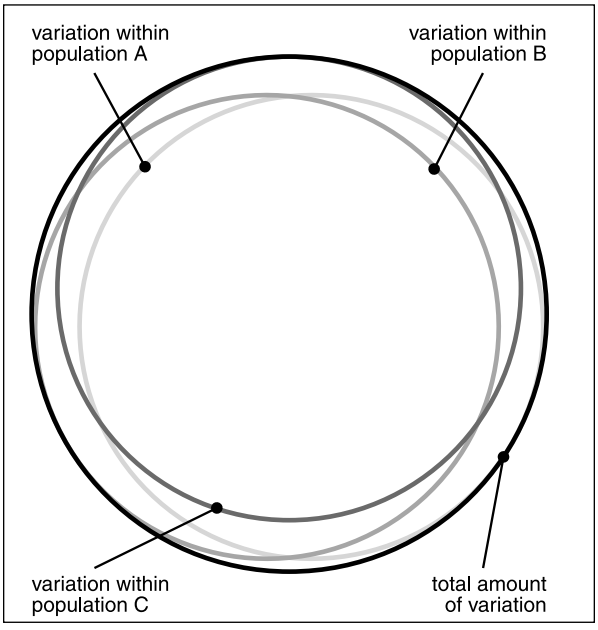


Figure 4 Most variation occurs within populations.

Geneticists have used the reality of evolutionary conservation to detect genetic variations associated with some cancers. For example, mutations in the genes responsible for repair of DNA mismatches that arise during DNA replication are associated with one form of colon cancer. These mismatched repair genes are conserved in evolutionary history all the way back to the bacterium *Escherichia coli*, where the genes are designated *Mut*l and *Mut*s. Geneticists suspected that this form of colon cancer was associated with a failure of mismatch repair, and they used the known sequences from the *E. coli* genes to probe the human genome for homologous sequences. This work led ultimately to the identification of a gene that is associated with increased risk for colon cancer.

What Is the Significance of Human Genetic Variation?

Almost all human genetic variation is relatively insignificant biologically; that is, it has no adaptive significance. Some variation (for example, a neutral mutation) alters the amino acid sequence of the resulting protein but produces no detectable change in its function. Other variation (for example, a silent mutation) does not even change the amino acid sequence. Furthermore, only a small percentage of the DNA sequences in the human genome are coding sequences (sequences that are ultimately translated into protein) or regulatory sequences (sequences that can influence the level, timing, and tissue specificity of gene expression). Differences that occur elsewhere in the DNA—in the vast majority of the DNA that has no known function—have no impact.

Some genetic variation, however, can be positive, providing an advantage in changing environments.

The classic example from the high school biology curriculum is the mutation for sickle hemoglobin, which in the heterozygous state provides a selective advantage in areas where malaria is endemic.

More recent examples include mutations in the *CCR5* gene that appear to provide protection against AIDS. The *CCR5* gene encodes a protein on the surface of human immune cells. HIV, the virus that causes AIDS, infects immune cells by binding to this protein and another protein on the surface of those cells. Mutations in the *CCR5* gene that alter its level of expression or the structure of the resulting protein can decrease HIV infection. Early research on one genetic variant indicates that it may have risen to high frequency in Northern Europe about 700 years ago, at about the time of the European epidemic of bubonic plague. This finding has led some scientists to hypothesize that the CCR5 mutation may have provided protection against infection by *Yersinia pestis*, the bacterium that causes plague. The fact that HIV and *Y. pestis* both infect macrophages supports the argument for selective advantage of this genetic variant.

The sickle cell and AIDS/plague stories remind us that the biological significance of genetic variation depends on the environment in which genes are expressed. It also reminds us that differential selection and evolution would not proceed in the absence of genetic variation within a species.

Some genetic variation, of course, is associated with disease, as classic single-gene disorders such as sickle cell disease, cystic fibrosis, and Duchenne muscular dystrophy remind us. Increasingly, research also is uncovering genetic variations associated with the more common diseases that are among the major causes of sickness and death in developed countries—diseases such as heart disease, cancer, diabetes, and psychiatric disorders such as schizophrenia and bipolar disease (manic-depression). Whereas disorders such as cystic fibrosis or Huntington disease result from the effects of mutation in a single gene and are evident in virtually all environments, the more common diseases result from the interaction of multiple genes and environmental variables. Such diseases therefore are termed **polygenic** and **multifactorial**. In fact, the vast majority of human traits, diseases or otherwise, are multifactorial.

The genetic distinctions between relatively rare single-gene disorders and the more common multifactorial diseases are significant. Genetic variations that underlie single-gene disorders generally are relatively recent, and they often have a major, detrimental impact, disrupting homeostasis in significant ways. Such disorders also generally exact their toll early in life, often before the end of childhood. In contrast, the genetic variations that underlie common, multifactorial diseases generally are of older origin and have a smaller, more gradual effect on homeostasis. They also generally have their onset in adulthood. The last two characteristics make the ability to detect genetic variations that predispose/increase risk of common diseases especially valuable because people have time to modify their behavior in ways that can reduce the likelihood that the disease will develop, even against a background of genetic predisposition.

How Is Our Understanding of Human Genetic Variation Affecting Medicine?

As noted earlier, one of the benefits of understanding human genetic variation is its practical value for understanding and promoting health and for understanding and combating disease. We probably cannot overestimate the importance of this benefit. First, as Figure 5 shows, virtually every human disease has a genetic component. In some diseases, such as Huntington disease, Tay-Sachs disease, and cystic fibrosis, this component is very large. In other diseases, such as cancer, diabetes, and heart disease, the genetic component is more modest. In fact, we do not typically think of these diseases as "genetic diseases," because we inherit not the certainty of developing a disease, but only a predisposition to developing it.

In still other diseases, the genetic component is very small. The crucial point, however, is that it is there. Even infectious diseases, diseases that we have traditionally placed in a completely different category

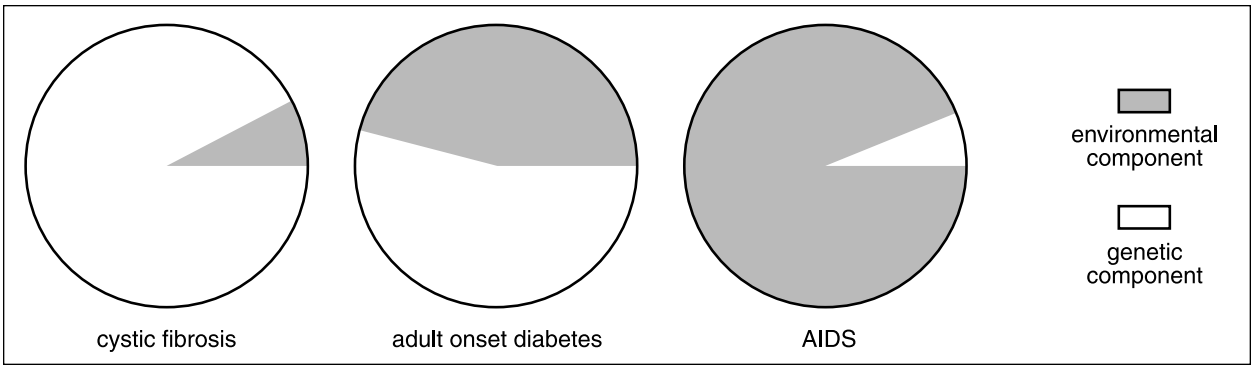


Figure 5 Virtually all human diseases, except perhaps trauma, have a genetic component.

than genetic disorders, have a real, albeit small, genetic component. For example, as the CCR5 example described earlier illustrates, even AIDS is influenced by a person's genotype. In fact, some people appear to have genetic resistance to HIV infection as a result of carrying a variant of the CCR5 gene.

Second, each of us is at some genetic risk, and therefore can benefit, at least theoretically, from the progress scientists are making in understanding and learning how to respond to these risks. Scientists estimate that each of us carries between 5 and 50 mutations that carry some risk for disease or disability. Some of us may not experience negative consequences from the mutations we carry, either because we do not live long enough for it to happen or because we may not be exposed to the relevant environmental triggers. The reality, however, is that the potential for negative consequences from our genes exists for each of us.

How is modern genetics helping us address the challenge of human disease? As Figure 6 shows, modern genetic analysis of a human disease begins with mapping and cloning the associated gene or genes. Some of the earliest disease genes to be mapped and cloned were the genes associated with Duchenne muscular dystrophy, retinoblastoma, and cystic fibrosis. More recently, scientists have announced the cloning of genes for breast cancer, diabetes, and Parkinson disease.

As Figure 6 also shows, mapping and cloning a disease-related gene opens the way for the development of a variety of new health care strategies. At one end of the spectrum are genetic tests intended to identify people at increased risk for the disease and recognize genotypic differences that have implications for effective treatment. At the other end are new drug and gene therapies that specifically target the biochemical mechanisms that underlie the disease symptoms or even replace, manipulate, or supplement nonfunctional genes with functional ones. Indeed, as Figure 6 suggests, we are entering the era of molecular medicine.

Genetic testing is not a new health care strategy. Newborn screening for diseases like PKU has been going on for 30 years in many states. Nevertheless, the remarkable progress scientists are making in mapping and cloning human disease genes brings with it the prospect for the development of more genetic tests in the future. The availability of such tests can have a significant impact on the way the public perceives a particular disease and can also change the pattern of care that people in affected families might seek and receive. For example, the identification of the *BRCA1* and *BRCA2* genes and the demonstration that particular variants of these genes are associated with an increased risk of breast and ovarian cancer have paved the way for the development of guidelines and protocols for testing individuals with a family history of these diseases. *BRCA1*, located on the long arm of chromosome 17, was the first to be isolated, and variants of this gene account for about 50 percent of all *inherited* breast cancer, or about 5 percent of *all* breast cancer. Variants of *BRCA2*, located on the long arm of chromosome 13, appear to account for about 30 to 40 percent of all inherited breast cancer.

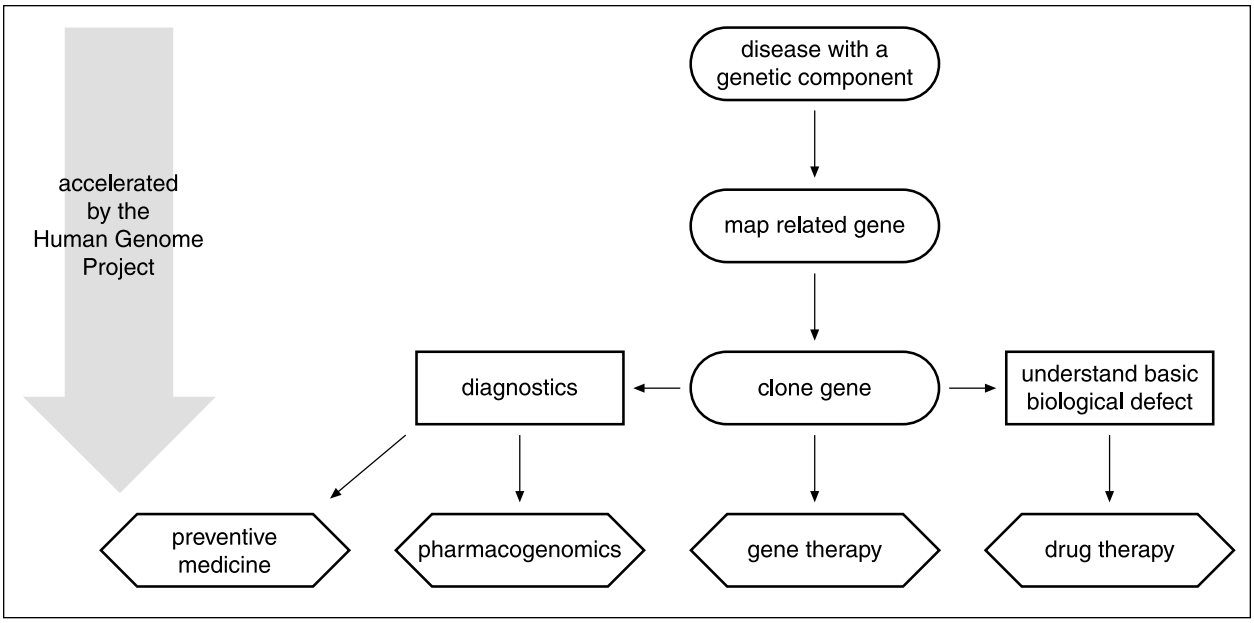


Figure 6 Mapping and cloning a gene can lead to strategies that reduce the risk of disease (preventive medicine); guidelines for prescribing drugs based on a person's genotype (pharmacogenomics); procedures that alter the affected gene (gene therapy); or drugs targeted at the biological mechanism that produces the disease symptoms (drug therapy). The Human Genome Project has accelerated the development of these strategies.

Variants of these genes also increase slightly the risk for men of developing breast, prostate, or possibly other cancers.

Scientists estimate that hundreds of thousands of women in the United States have 1 of hundreds of significant mutations already detected in the *BRCA1* gene. For a woman with a family history of breast cancer, the knowledge that she carries one of the variants of *BRCA1* or *BRCA2* associated with increased risk can be important information. If she does carry one of these variants, she and her physician can consider several changes in her health care, such as increasing the frequency of physical examinations; introducing mammography at an earlier age; and even having prophylactic mastectomy. In the future, drugs may also be available that decrease the risk of developing breast cancer.

The ability to test for the presence in individuals of particular gene variants is also changing the way drugs are prescribed and developed. A rapidly growing field known as **pharmacogenomics** focuses on crucial genetic differences that cause drugs to work well in some people and less well, or with dangerous adverse reactions, in others. For example, researchers investigating Alzheimer disease have found that the way patients respond to drug treatment can depend on which of three genetic variants of the *ApoE* (Apolipoprotein E) gene a person carries. Likewise, some of the variability in children's responses to therapeutic doses of albuterol, a drug used to treat asthma, was recently linked to genotypic differences in the beta-2-adrenergic receptor. Because beta-2-adrenergic receptor agonists (of which albuterol is one) are the most widely used agents in the treatment of asthma, these results may have profound implications for understanding the genetic factors that determine an individual's response to asthma therapy.

Experts predict that increasingly in the future, physicians will use genetic tests to match drugs to an individual patient's body chemistry, so that the safest and most effective drugs and dosages can be prescribed. After identifying the genotypes that determine individual responses to particular drugs, pharmaceutical companies also likely will set out to develop new, highly specific drugs and revive older ones whose effects seemed in the past too unpredictable to be of clinical value.

Knowledge of the molecular structure of disease-related genes also is changing the way researchers approach developing new drugs. A striking example followed the discovery in 1989 of the gene associated with cystic fibrosis (CF). Researchers began to study the function of the normal and defective proteins involved in order to understand the biochemical consequences of the gene's variant forms and to develop new treatment strategies based on that knowledge. The normal protein, called CFTR for cystic fibrosis transmembrane conductance regulator, is embedded in the membranes of several cell types in the body, where it serves as a channel, transporting chloride ions out of the cells. In CF patients, depending on the particular mutation the individual carries, the CFTR protein may be reduced or missing from the cell membrane, or may be present but not function properly. In some mutations, synthesis of CFTR protein is interrupted, and the cells produce no CFTR molecules at all.

Although all of the mutations associated with CF impair chloride transport, the consequences for patients with different mutations vary. For example, patients with mutations causing absent or markedly reduced CFTR protein may have more severe disease than patients with mutations in which CFTR is present but has altered function. The different mutations also suggest different treatment strategies. For example, the most common CF-related mutation (called delta F508) leads to the production of protein molecules (called delta F508 CFTR) that are misprocessed and are degraded prematurely before they reach the cell membrane. This finding suggests that drug treatments that would enhance transport of the defective delta F508 protein to the cell membrane or prevent its degradation could yield important benefits for patients with delta F508 CFTR.

Finally, the identification, cloning, and sequencing of a disease-related gene can open the door to the development of strategies for treating the disease using the instructions encoded in the gene itself. Collectively referred to as **gene therapy**, these strategies typically involve adding a copy of the normal variant of a disease-related gene to a patient's cells. The most familiar examples of this type of gene therapy are cases in which researchers use a vector to introduce the normal variant of a disease-related gene into a patient's cells and then return those cells to the patient's body to provide the function that was missing. This strategy was first used in the early 1990s to introduce the normal allele of the adenosine deaminase (ADA) gene into the body of a little girl who had been born with ADA deficiency. In this disease, an abnormal variant of the ADA gene fails to make adenosine deaminase, a protein that is required for the correct functioning of T-lymphocytes.

Although researchers are continuing to refine this general approach to gene therapy, they also are developing new approaches. For example, scientists hope that one very new strategy, called chimeraplasty, may one day be used to actually *correct* genetic defects that involve only a single base change. Chimeraplasty uses specially synthesized molecules that base pair with a patient's DNA and stimulate the cell's normal DNA repair mechanisms to remove the incorrect base and substitute the correct one. At this point, chimeraplasty is still in early development and the first clinical trials are about to get underway.

Yet another approach to gene therapy involves providing new or altered functions to a cell through the introduction of new genetic information. For example, recent experiments have demonstrated that it is possible, under carefully controlled experimental conditions, to introduce genetic information into cancer cells that will alter their metabolism so that they commit suicide when exposed to a normally innocuous environmental trigger. Researchers are also using similar experiments to investigate the feasibility of introducing genetic changes into cells that will make them immune to infection by HIV. Although this research is currently being done only in nonhuman primates, it may eventually benefit patients infected with HIV.

As Figure 6 indicates, the Human Genome Project (HGP) has significantly accelerated the pace of both the discovery of human genes and the development of new health care strategies based on a knowledge

of a gene's structure and function. The new knowledge and technologies emerging from HGP-related research also are reducing the cost of finding human genes. For example, the search for the gene associated with cystic fibrosis, which ended in 1989, before the inception of the HGP, required more than eight years and $50 million. In contrast, finding a gene associated with a Mendelian disorder now can be accomplished in less than a year at a cost of approximately $100,000.

The last few years of research into human genetic variation also have seen a gradual transition from a primary focus on genes associated with single-gene disorders, which are relatively rare in the human population, to an increasing focus on genes associated with multifactorial diseases. Because these diseases are not rare, we can expect that this work will affect many more people. Understanding the genetic and environmental bases for these multifactorial diseases also will lead to increased testing and the development of new interventions that likely will have an enormous effect on the practice of medicine in the next century.

Genetics, Ethics, and Society

What are the implications of using our growing knowledge of human genetic variation to improve personal and public health? As noted earlier, the rapid pace of the discovery of genetic factors in disease has improved our ability to predict the risk of disease in asymptomatic individuals. We have learned how to prevent the manifestations of some of these diseases, and we are developing the capacity to treat others.

Yet, much remains unknown about the benefits and risks of building an understanding of human genetic variation at the molecular level. While this information would have the potential to dramatically improve human health, the architects of the HGP realized that it also would raise a number of complex ethical, legal, and social issues. Thus, in 1990 they established the Ethical, Legal, and Social Implications (ELSI) program to anticipate and address the ethical, legal, and social issues that arise from human genetic research. This program, perhaps more than any other, has focused public attention, as well as the attention of educators, on the increasing importance of preparing citizens to understand and contribute to the ongoing public dialogue related to advances in genetics.

Ethics is the study of right and wrong, good and bad. It has to do with the actions and character of individuals, families, communities, institutions, and societies. During the last two and one-half millennia, Western philosophy has developed a variety of powerful methods and a reliable set of concepts and technical terms for studying and talking about the ethical life. Generally speaking, we apply the terms "right" and "good" to those actions and qualities that foster the interests of individuals, families, communities, institutions, and society. Here, an "interest" refers to a participant's share or participation in a situation. The terms "wrong" or "bad" apply to those actions and qualities that impair interests.

Ethical considerations are complex, multifaceted, and raise many questions. Often, there are competing, well-reasoned answers to questions about what is right and wrong, and good and bad, about an individual's or group's conduct or actions. Typically, these answers all involve appeals to values. A **value** is something that has significance or worth in a given situation. One of the exciting events to witness in any discussion in ethics is the varying ways in which the individuals involved assign values to things, persons, and states of affairs. Examples of values that students may appeal to in a discussion about ethics include autonomy, freedom, privacy, sanctity of life, religion, protecting another from harm, promoting another's good, justice, fairness, relationships, scientific knowledge, and technological progress.

Acknowledging the complex, multifaceted nature of ethical discussions is not to suggest that "anything goes." Experts generally agree on the following features of ethics. First, ethics is a process of rational inquiry. It involves posing clearly formulated questions and seeking well-reasoned answers to those questions. For example, we can ask questions about an individual's right to privacy regarding personal genetic information; we also can ask questions about the appropriateness of particular uses of gene therapy. Well-reasoned answers to such questions constitute

arguments. Ethical analysis and argument, then, result from successful ethical inquiry.

Second, ethics requires a solid foundation of information and rigorous interpretation of that information. For example, one must have a solid understanding of biology to evaluate the recent decision by the Icelandic government to create a database that will contain extensive genetic and medical information about the country's citizens. A knowledge of science also is needed to discuss the ethics of genetic screening or of germ-line gene therapy. Ethics is not strictly a theoretical discipline but is concerned in vital ways with practical matters.

Third, discussions of ethical issues often lead to the identification of very different answers to questions about what is right and wrong and good and bad. This is especially true in a society such as our own, which is characterized by a diversity of perspectives and values. Consider, for example, the question of whether adolescents should be tested for late-onset genetic conditions. Genetic testing centers routinely withhold genetic tests for Huntington disease (HD) from asymptomatic patients under the age of 18. The rationale is that the condition expresses itself later in life and, at present, treatment is unavailable. Therefore, there is no immediate, physical health benefit for a minor from a specific diagnosis based on genetic testing. In addition, there is concern about the psychological effects of knowing that later in life one will get a debilitating, life-threatening condition. Teenagers can wait until they are adults to decide what and when they would like to know. In response, some argue that many adolescents and young children do have sufficient autonomy in consent and decision making and may wish to know their future. Others argue that parents should have the right to have their children tested, because parents make many other medical decisions on behalf of their children. This example illustrates how the tools of ethics can bring clarity and rigor to discussions involving values.

One of the goals of this module is to help students see how understanding science can help individuals and society make reasoned decisions about issues related to genetics and health. Activity 5, *Making Decisions in the Face of Uncertainty*, presents students with a case of a woman who is concerned that she may carry an altered gene that predisposes her to breast and ovarian cancer. The woman is faced with numerous decisions, which students also consider. Thus, the focus of Activity 5 is prudential decision making, which involves the ability to avoid unnecessary risk when it is uncertain whether an event actually will occur. By completing the activity, students understand that uncertainty is often a feature of questions related to genetics and health, because our knowledge of genetics is incomplete and constantly changing. In addition, students see that making decisions about an uncertain future is complex. In simple terms, students have to ask themselves, "How bad is the outcome and how likely is it to occur?" When the issues are weighed, different outcomes are possible, depending on one's estimate of the incidence of the occurrence and how much burden one attaches to the risk.

Clearly, science as well as ethics play important roles in helping individuals make choices about individual and public health. Science provides evidence that can help us understand and treat human disease, illness, deformity, and dysfunction. And ethics provides a framework for identifying and clarifying values and the choices that flow from these values. But the relationships between scientific information and human choices, and between choices and behaviors, are not straightforward. In other words, human choice allows individuals to choose against sound knowledge, and choice does not require action.

Nevertheless, it is increasingly difficult to deny the claims of science. We are continually presented with great amounts of relevant scientific and medical knowledge that is publicly accessible. As a consequence, we can think about the relationships between knowledge, choice, behavior, and human welfare in the following ways:

knowledge (what is and is not known) + choice = power

power + behavior = increased human welfare (that is, personal and public health)

One of the goals of this module is to encourage students to think in terms of these relationships, now and as they grow older.

Implementing the Module

The five activities in this module are designed to be taught either in sequence, as a supplement to your standard curriculum, or as individual activities that support or enhance your treatment of specific concepts in biology. The following pages offer general suggestions about using these materials in the classroom; you will find specific suggestions in the support material provided for each activity.

Goals for the Program

Human Genetic Variation is designed to help students develop the following major goals associated with biological literacy: (1) to understand a set of basic scientific principles related to human genetic variation, (2) to experience the process of inquiry and develop an enhanced understanding of the nature and methods of science, and (3) to recognize the role of science in society and the relationship between basic science and personal and public health.

Conceptual Organization of the Activities

We have organized the activities to form a conceptual whole that moves students from an introduction to human genetic variation (*Alike, But Not the Same*), to an investigation of its biological significance (*The Meaning of Genetic Variation*), to a discussion of some of the practical implications of human genetic variation for the treatment of disease (*Molecular Medicine Comes of Age* and *Are You Susceptible?*) and, finally, to a consideration of how understanding human genetic variation can affect the decisions we make about our own health

Figure 7 Conceptual Flow of the Activities

Activity	Major Concept
Activity 1 *Alike, But Not the Same*	Humans share many basic characteristics, but there is a wide range of variation in human traits. Most human traits are multifactorial: They are influenced by multiple genes and environmental factors.
Activity 2 *The Meaning of Genetic Variation*	The ultimate source of genetic variation is differences in DNA sequences. Most of those genetic differences do not affect how individuals function. Some genetic variation, however, is associated with disease, and some improves the ability of the species to survive changes in the environment. Genetic variation, therefore, is the basis for evolution by natural selection.
Activity 3 *Molecular Medicine Comes of Age*	One of the benefits of understanding human genetic variation at a molecular level is its practical value for helping us understand and treat disease. The development of effective gene-based therapies is an exciting outcome of human genetic research. These therapies, however, are potentially many years away for many diseases.
Activity 4 *Are You Susceptible?*	Studying the genetic and environmental factors involved in multifactorial diseases will lead to increased diagnosis, prevention, and treatment of disease.
Activity 5 *Making Decisions in the Face of Uncertainty*	Our growing understanding of human genetic variation will allow us to identify genes that are associated with common diseases such as cancer. Genetic testing to identify individuals who have variations that make them susceptible to certain diseases can help people make decisions in uncertain circumstances and holds the prospect for more effective prevention and treatment. However, this capability also raises difficult questions that illustrate the personal and social implications of biological research.

(*Making Decisions in the Face of Uncertainty*). Figure 7 illustrates the sequence of major concepts addressed by the five activities.

Although we encourage you to use the activities in the sequence outlined in Figure 7, many of the activities can be taught individually, to replace or enhance a more traditional approach to the same or related content. Figure 8 provides recommendations for inserting the activities into a standard high school curriculum in biology.

Correlation to the *National Science Education Standards*

Human Genetic Variation supports teachers in their efforts to reform science education in the spirit of the National Research Council's 1996 *National Science Education Standards* (*NSES*). Figure 9 lists the specific content and teaching standards that this module primarily addresses.

Active, Collaborative, and Inquiry-Based Learning

The activities in this module are designed to offer students the opportunity to participate in active, collaborative, and inquiry-based learning in biology. But what do these terms mean? Despite their current popularity, many teachers think of active, collaborative, and inquiry-based learning rather generically. Defining these three key terms more specifically will provide a foundation on which we can build a detailed description of the instructional approach that the five activities in this module advocate and implement.

Conceptually the broadest of the three, **active learning** means that students are involved "in doing things and thinking about the things they are doing" (Bonwell and Eison, 1991, p. 2). These authors elaborate by listing the following characteristics typically

Figure 8 Correlation Between Activities and Standard Curricula*

Topic	Module Activity					Biology Textbook** Chapter									
	1	2	3	4	5	DOL	AEE	LS	Blue	Green	Human	VL	P & E	Modern	TLS
evolution and natural selection		•				18	29	12	16	9	2	10	12	15	10, 11
ethical issues related to genetic testing and screening		•	•	•	•	15	–	9	13	8	11 essay, 12	10	12, 13	7, 9	7, 9
human genetic variation including genetic disorders		•				15	26, 27	11	13	8	11	7	12	7	7
multifactorial traits	•	•	•	•	•	14	–	–	12, 13	8	11	7	12	6	6

*The table indicates where topics addressed in the module are covered in a variety of current high school textbooks.

**DOL = *Biology: The Dynamics of Life* (Glencoe)
AEE = *Biology: An Everyday Experience* (Glencoe)
LS = *Biology: Living Systems* (Glencoe)
Blue = *BSCS Biology: A Molecular Approach* (D.C. Heath and Co./McDougal-Littel)
Green = *BSCS Biology: An Ecological Approach* (Kendall/Hunt)
Human = *BSCS Biology: A Human Approach* (Kendall/Hunt)
VL = *Biology: Visualizing Life* (Holt, Rinehart, Winston)
P & E = *Biology: Principles & Explorations* (Holt, Rinehart, Winston)
Modern = *Modern Biology* (Holt, Rinehart, Winston)
TLS = *Biology: The Living Science* (Prentice Hall)

Figure 9 Correlation to the *National Science Education Standards*

The Content Standards	
Standard A: As a result of activities in grades 9–12, all students should develop abilities necessary to do scientific inquiry and understandings about scientific inquiry.	**Correlation to *Human Genetic Variation***
• Identify questions and concepts that guide scientific investigations.	Activities 1, 2, and 3
• Use technology and mathematics to improve investigations and communications.	Activity 2
• Formulate and revise scientific explanations and models using logic and evidence.	Activities 2 and 3
• Recognize and analyze alternative explanations and models.	Activities 2 and 3
• Communicate and defend a scientific argument.	Activity 3
• Understandings about scientific inquiry.	Activities 2 and 3
Standard C: As a result of their activities in grades 9–12, all students	**Correlation to *Human Genetic Variation***
should develop understanding of the cell.	
• Cells store and use information to guide their functions.	Activities 2, 3, and 5
• Cells can differentiate, and complex multicellular organisms are formed as a highly organized arrangement of differentiated cells.	Activities 2 and 5
should develop understanding of the molecular basis of heredity.	
• In all organisms, the instructions for specifying the characteristics of the organism are carried in the DNA.	Activities 2, 3, and 5
• Changes in DNA occur spontaneously at low rates.	Activities 2, 3, and 5
should develop understanding of biological evolution.	
• Species evolve over time.	Activity 2
Standard E: As a result of activities in grades 9–12, all students should develop abilities of technological design and understandings about science and technology.	**Correlation to *Human Genetic Variation***
• Scientists in different disciplines ask different questions, use different methods of investigation, and accept different types of evidence to support these explanations.	Activity 3
• Science often advances with the introduction of new technologies.	Activity 5
• Creativity, imagination, and a good knowledge base are all required in the work of science and engineering.	Activities 1–5
• Science and technology are pursued for different purposes.	Activity 5

Standard F: As a result of activities in grades 9–12, all students should develop understanding of	**Correlation to *Human Genetic Variation***
• personal and community health.	Activities 2, 3, 4, and 5
• natural and human-induced hazards.	Activities 2, 3, 4, and 5
• science and technology in local, national, and global challenges.	Activity 5
Standard G: As a result of activities in grades 9–12, all students should develop understanding of	**Correlation to *Human Genetic Variation***
• science as a human endeavor.	Activity 3
• nature of scientific knowledge.	Activities 1–5
• historical perspectives.	Activity 2
The Teaching Standards	
Standard A: Teachers of science plan an inquiry-based science program for their students. In doing this, teachers	**Correlation to *Human Genetic Variation***
• develop a framework of yearlong and short-term goals for students.	Each activity provides short-term objectives for students. Figures 7, Conceptual Flow of the Activities, and 13, Timeline for Teaching the Module, also help teachers plan.
• select science content and adapt and design curriculum to meet the interests, knowledge,understanding, abilities, and experiences of students.	Using the module helps teachers update their curriculum in response to their students' interest in this topic.
• select teaching and assessment strategies that support the development of student understanding and nurture a community of science learners.	The focus on active, collaborative, and inquiry-based learning in the activities helps teachers meet this standard.
Standard B: Teachers of science guide and facilitate learning. In doing this, teachers	**Correlation to *Human Genetic Variation***
• focus and support inquiries while interacting with students.	All of the activities in the module encourage and support student inquiry.
• orchestrate discourse among students about scientific ideas.	All of the activities in the module promote discourse among students.
• challenge students to accept and share responsibility for their own learning.	All of the activities in the module challenge students to accept and share responsibility for their learning.
• recognize and respond to student diversity and encourage all students to participate fully in science learning.	Combining the 5E instructional model with active, collaborative learning is an effective way of responding to the diversity of student backgrounds and learning styles.
• encourage and model the skills of scientific inquiry, as well as the curiosity, openness to new ideas and data, and skepticism that characterize science.	Annotations for the teacher that occur throughout the activities provide many suggestions for how teachers can model these attributes.

Standard C: Teachers of science engage in ongoing assessment of their teaching and of student learning. In doing this, teachers	**Correlation to *Human Genetic Variation***
• use multiple methods and systematically gather data about student understanding and ability.	Each activity has a variety of assessment components embedded within its structure. Annotations draw teachers' attention to these opportunities for assessment.
• analyze assessment data to guide teaching.	Annotations provide answers to questions that can help teachers analyze student feedback. The annotations also suggest ways for teachers to change their approach to students, based on that feedback.
Standard E: Teachers of science develop communities of science learners that reflect the intellectual rigor of scientific inquiry and the attitudes and social values conducive to science learning. In doing this, teachers	**Correlation to *Human Genetic Variation***
• display and demand respect for the diverse ideas, skills, and experiences of all students.	The answers provided for teachers model these qualities.
• nurture collaboration among students.	All of the activities are designed to be completed by students working in collaborative teams.
• structure and facilitate ongoing formal and informal discussion based on a shared understanding of rules of scientific discourse.	All of the discussions in the activities model the rules of scientific discourse.
• model and emphasize the skills, attitudes, and values of scientific inquiry.	The annotations for teachers provide many suggestions about how to model these skills, attitudes, and values.

associated with strategies that deserve to be labeled "active:"

- Students are involved in more than listening.
- ÄInstructors place less emphasis on transmitting information and more emphasis on developing students' skills.
- Students are involved in higher-order thinking (for example, analysis, synthesis, and evaluation).
- Students are engaged in activities (for example, reading, discussing, and writing).
- Instructors encourage students' exploration of their own understandings, attitudes, and values.

Most teachers endorse the use of active learning. We know intuitively, if not experientially and explicitly, that learning does not occur through pas sive absorption. But often we do not realize *how active* students must be for real learning to occur. Typically, the answer to this question is *more active* than we might expect.

The activities in this module were designed with the following assumptions about active learning (BSCS, 1999):

1. An activity promotes active learning to the degree to which *all students,* not simply a vocal few, are involved in mental processing related to the content.
2. An activity promotes active learning to the degree that it offers *extended opportunities* for stu dents to become personally engaged with the content.
3. An activity promotes active learning to the degree that it involves students in thinking *deeply* about content.

The activities also make extensive use of **collabora tive learning**. Most often occurring within the context of group work, collaborative and cooperative learning currently enjoy "favorite child" status among the many strategies available to teachers.

Teachers are using group approaches across disci plines, for in- and out-of-class assignments, with large and small classes, and with beginning and advanced students. In fact, you will often find that collaborative activities go hand-in-hand with active learning.

Collaborative and cooperative learning, both with long theoretical and empirical histories, come out of different academic traditions, operate on different premises, and employ different strategies. But both approaches share a fundamental commitment to the notion that students learn from and with each other, "learning through joint intellectual effort," according to one expert (Brody, 1995, p. 134). In the interest of brevity, we will leave undiscussed the finer distinctions between the two, offering in this curriculum a mix of strategies that put students together and engage them in tasks that encourage learning in collective contexts.

Finally, the activities in the module use **inquiry-based strategies**. All truly inquiry-based activities share the characteristics of active learning. In addi tion, inquiry-based strategies emphasize discovery: the process of observation, followed by analysis, that leads to explanation, to conclusion, or to the next question. Note that an activity need not involve students in active experimentation to be fundamentally an inquiry experience.

More than active or collaborative learning, inquiry-based strategies attempt to teach students how biol ogists see the world, how they think about what they see, and how they draw conclusions that are consistent with observations and current knowl edge. Such strategies say to the student, in effect, "*This* is science as a way of knowing."

The 5E Instructional Model

The activities in the module also have been designed using an instructional model to organize and sequence the experiences offered to students. This model, called the 5E model, is based on **constructivism**, a term that expresses a view of the student as an active agent who "constructs" meaning out of his or her interac tions with events (Perkins, 1992). According to this view, rather than passively absorbing information, the student redefines, reorganizes, elaborates, and changes his or her initial understandings through interactions with phenomena, the environment, and other individuals. In short, the student inter prets objects and phenomena and then internalizes this interpretation in terms of previous experiences.

A constructivist view of learning recognizes that the development of ideas and the acquisition of lasting understandings take time and experiences (Saunders, 1992). In the typical classroom, this means that fewer concepts and subjects can be cov ered during the school year or, in this case, in five days of instruction. Nevertheless, research suggests that students who are given time and opportunity to thoroughly grasp a small number of important concepts do better on traditional tests than students who are exposed briefly to a large number of ideas (Sizer, 1992; Knapp, 1995). In fact, the intensive thinking involved in constructing a thorough understanding of a few major ideas appears to ben efit all students, regardless of ability.

Figure 10 illustrates the key components of the 5E model, so-called because it takes students through five phases of learning that are easily described using five words that begin with the let ter "E": Engage, Explore, Explain, Elaborate, and Evaluate.

This instructional model allows students to share common experiences related to human genetic vari ation, to use and build on prior knowledge, to con struct meaning, and to assess continually their understanding of a major concept. It avoids exces sive use of lecture because research shows that 10 minutes of lecture is near the upper limit of com fortable attention that students give to lecture mate-rial, whereas the attention span in an investigative activity is far longer (Project Kaleidoscope, 1991). In the 5E model, the teacher acts as facilitator and coach much more frequently than he or she acts as the disseminator of information.

The following paragraphs illustrate how the 5Es are implemented across the activities in this module. They also provide suggestions about effective teaching behaviors that help students experience each phase of the learning cycle.

Figure 10 The Key Components of the 5E Model

Phase 1	What the Teacher Does That Is	
	***Consistent* with the 5E Model**	***Inconsistent* with the 5E Model**
Engage	Creates interest Generates curiosity Raises questions Elicits responses that uncover what students know or think about the concept/subject	Explains concepts Provides definitions and answers States conclusions Provides premature answers to students' questions Lectures
Explore	Encourages students to work together without direct instruction from teacher Observes and listens to students as they interact Asks probing questions to redirect students' investigations when necessary Provides time for students to puzzle through problems Acts as a consultant for students	Provides answers Tells or explains how to work through the problem Tells students they are wrong Gives information or facts that solve the problem Leads students step-by-step to a solution
Explain	Encourages students to explain concepts and definitions in their own words Asks for justification (evidence) and clarification from students Formally provides definitions, explanations, and new labels Uses students' previous experiences as the basis for explaining concepts	Accepts explanations that have no justification Neglects to solicit students' explanations Introduces unrelated concepts or skills
Elaborate	Expects students to use formal labels, definitions, and explanations provided previously Encourages students to apply or extend concepts and skills in new situations Reminds students of alternative explanations Refers students to existing data and evidence and asks, "What do you already know?" "Why do you think . . . ?"	Provides definitive answers Tells students they are wrong Lectures Leads students step-by-step to a solution Explains how to work through the problem
Evaluate	Observes students as they apply new concepts and skills Assesses students' knowledge and/or skills Looks for evidence that students have changed their thinking or behaviors Allows students to assess their own learning and group-process skills Asks open-ended questions, such as "Why do you think . . . ?" "What evidence do you have?" "What do you know about x?" "How would you explain x?"	Test vocabulary words, terms, and isolated facts Introduces new ideas or concepts Creates ambiguity Promotes open-ended discussion unrelated to concept or skill

Activity 1, *Alike, But Not the Same*, serves as the Engage phase of instruction for the students. This phase initiates the learning sequence and introduces the major topic to be studied. Its primary purpose is to capture the students' attention and interest. The activity is designed to make connections between past and present learning experiences and to anticipate upcoming activities. By completing it, students should become mentally engaged in the topic of human genetic variation and should begin to think about how it relates to their previous experiences. Successful engagement results in students who are intrigued by the con cepts they are about to study in depth.

Activity 2, *The Meaning of Genetic Variation*, serves in a broad sense as the Explore phase of the model. In this activity, students ask and answer questions about the ways in which human variation might be significant, and then use resources on the CD-ROM to explore its significance as the basis for evolution by natural selection.

Molecular Medicine Comes of Age, Activity 3, moves students into the Explain phase of the model. During this phase, students look more closely at the molecular basis for human genetic variation and develop a more detailed set of explanations for the concepts they have been exploring. Explain activities give students opportunities to articulate their developing conceptual understanding or to demonstrate particular skills or behaviors. Typically, this is where the teacher introduces relevant terms and definitions, and where students might do some assigned reading about defined topics. Keep in mind, however, that Explain activities still are *student*-centered. In Activity 3, the students develop their own explanations for how studying human genetic variation at a molecular level is changing the practice of medicine. Here, the teacher's role is to guide students so that they have ample opportunity to develop a more complete understanding of this phenomenon.

During the Elaborate phase of the model, exemplified in this module by Activity 4, *Are You Susceptible?*, students are challenged to extend their understanding of human genetic variation. Through a new set of questions and experiences, the students develop a deeper, broader understanding of the topic, obtain more information about areas of interest, and refine their scientific and critical-thinking skills. A teacher's primary goal in this phase of the model is to help students articulate generalizations and extensions of concepts and understandings that are relevant to their lives.

Finally, Activity 5, *Making Decisions in the Face of Uncertainty*, acts as the Evaluate activity for the program. At this point, it is important that students see that they can use their understanding of human genetic variation in the real world. It also is important that they receive some feedback on the adequacy of their explanations and understandings. Evaluate activities are complex and challenging, and Activity 5 will stretch your students' abilities to listen, think, and speak.

Using the *Human Genetic Variation* CD-ROM in the Classroom

The *Human Genetic Variation* CD-ROM that accompanies this module is a tool, like an overhead projector or a textbook, that you can use to help organize your use of the module, engage student interest in learning, and help orchestrate and individualize instruction. The CD-ROM contains the following major resources:

- introductions to the National Institutes of Health and National Human Genome Research Institute;
- printable files of this module;
- printable files of the print-based alternatives for Activities 2 and 5;
- video documentary and reference database required to complete Activity 2, *The Meaning of Genetic Variation*;
- optional video clips in support of Activity 3, *Molecular Medicine Comes of Age*; and
- the video clips and reference database required to complete Activity 5, *Making Decisions in the Face of Uncertainty*.

The CD-ROM runs on Apple Macintosh and IBM-compatible personal computers. The recommended requirements for a Macintosh computer are the following: OS 7.1 operating system or higher, 68030 or Power Mac processor, 256 color monitor or higher, 8 megabytes RAM, QuickTime 4 for Macintosh, and a 2x CD-ROM.

The recommended requirements for IBM-compatible computers are the following: Windows 95 operating system or higher, Pentium 60 processor or higher, 256 color monitor or higher, 8 megabytes RAM, Soundblaster or Windows Sound System-compatible card, QuickTime 4 for Windows, and a 2x CD-ROM.

To use the CD-ROM, load it into the CD-ROM drive as you would any other CD. If you do not have QuickTime 4 loaded on your computer, you will see a dialogue box that will ask if you want to install it. Click Yes to automatically load the program. Then, follow the installation instructions shown in Figure 11.

Figure 11 Loading Instructions for the *Human Genetic Variation* CD-ROM

IBM-Compatible Computers

Place the CD in the CD-ROM drive and close the door. The CD should automatically launch the program.

If you have turned off the autorun feature on your CD-ROM drive, you must run the setup program the first time you use the software. Click Start | Run and type the following into the dialog box:

d:\setup.exe (change "d:\" depending on the letter of your CD-ROM drive)

If you want to run the software without ejecting and re-inserting the disk each time you use the program, do one of the following:

- Click Start | Programs | NIH Supplements | NIH CD-ROM
- Click Start | Run and type the following in the dialog box:
  d:\hsplayer\hsplayer.exe home.stk
  (change "d:\" if necessary). Click OK.

Macintosh Computers

Place the CD in the CD-ROM drive and close the door.

Open the CD-ROM, then click on the NHGRI icon.

Network Installation

A network installation of the entire program requires up to 250 to 450 megabytes of disk space. Performance of the videos will depend on the network speed and the processor speed of client stations. Each client computer must have QuickTime 4 or higher installed.

1. Place the disk in the CD-ROM drive and click on Quit if the program opens automatically.
2. Create a folder on the network or local drive where you want to install the application and name it Variation.
3. Copy all the folders and files in the root directory of the CD-ROM into the new folder. Note: Macintosh users cannot see files from the PC format on the CD-ROM and vice versa. If you run both platforms from your network, you need to copy files from the CD to the network twice, once from a network PC and once from a network Mac. If you have room, create two complete copies of the software in different folders, one for each platform. Because users will see both Mac and PC files on the network, be sure that Mac users open only the Mac files and PC users open only the PC files.
4. To run the application, follow the procedures described, left, for IBM-compatible or Macintosh computers by locating the local or network copy of the desired HyperStudio player files.

The ideal use of the CD-ROM requires one computer for each student team; the installation instructions explain how to make the information available over a network. However, if you have only one computer and CD-ROM drive available, you can still use the CD (for example, by using a suitable display device to show animations or videos to the whole class or by rotating teams through a computer station to access CD-ROM-based resources).

If you do not have the facilities for using the CD-ROM in your classroom, a print-based alternative for each activity that requires the CD is available for printing from the CD-ROM. To use this version, you will need to print out the activity lesson plan and its associated masters.

Before you use this CD-ROM or any other piece of instructional software in your classroom, it may be valuable to identify some of the benefits you expect the software to provide. For example, Roblyer (1997) suggests four major ways that instructional multimedia software can benefit students and teachers. First, well-designed multimedia software can **help motivate students**, help them enjoy learning, and help them want to learn more. Multimedia programs offer users a rich,

interesting, and compelling environment in which to explore and learn, and it rewards users with a broader and more complex set of sensory experiences than print-based resources can provide. Well-designed multimedia resources can enliven content that students otherwise may perceive as dull and uninteresting. The video clips provided on the *Human Genetic Variation* CD offer students this benefit. Because they provide nonlinear access to a rich array of information and stimulation, multimedia programs also can encourage reluctant students to immerse themselves in a topic, creating, in effect, a positive feedback loop in which students learn as they "go their own way," wherever their interest or curiosity takes them.

Second, well-designed multimedia software also **offers unique instructional capabilities**. For example, such software can stimulate students to explore topics in greater depth and in more different dimensions than students often are willing or able to pursue. The reference databases that support Activities 2 and 5 have this effect. This benefit is related to the first, but it deepens and intensifies learning rather than stimulates students to investigate content they otherwise would not investigate. Part of this benefit derives from the power such software has to provide essentially immediate access to a wealth of ever more detailed and complex information on a topic, all presented in interesting and unusual ways. Part of the benefit, however, derives from the software's very design. A well-designed user interface provides an easy-to-use navigation system, stimulates curiosity, and encourages exploration of related areas.

Completing activities using instructional software can help students learn to organize and be responsible for their own learning rather than depend entirely on the teacher for direction and support. This goal is commonly cited by teachers and employers, most of whom explicitly desire students and employees who are self-directed and can structure and execute work independently.

Multimedia software can offer students learning experiences that are closer to actual field experiences than the experiences print-based resources offer. The videos that support Activity 5 allow students to listen to people advocating real positions on the topic under investigation. Although the student's experience of the situation in Activity 5 is vicarious, it is more realistic and memorable than the comparatively static and unchanging experience a script of this story would offer. Because it engages more senses than simply sight, and because it requires more skills than simply understanding what one reads, well-designed instructional software also addresses many different learning styles and serves the needs of a wider population of students than most print-based resources.

Third, multimedia software can provide teachers with **support for experimenting with new instructional approaches**. The educational system in the United States is struggling to improve its ability to prepare students for the complex, collaborative, technology-rich workplace they will enter when they leave school. Technology can make possible new approaches to teaching in the classroom. For example, by moving the responsibility for organizing learning from the teacher to the student, instructional software can help teachers move into the role of observer and facilitator of learning rather than dispenser of information. As students work independently or in small teams, teachers can circulate throughout the room, listening to students interact with one another, asking and answering questions, and challenging students to consider alternative lines of research and analysis. These behaviors are very different from the typical ones teachers are engaged in when they carry the primary responsibility for delivering and explaining content.

Instructional software also can be an effective tool for helping teachers organize discussions of controversial issues in the classroom. In Activity 5 in this module, using videos to present conflicting positions may lend greater credibility to these positions than if they were presented by the teacher. It also depersonalizes the positions, allowing both teachers and students to focus on the substance of the issues rather than on the controversy itself.

Software programs on CD-ROM also offer teachers the opportunity to expand and enrich the number

and depth of research-based projects they assign students, and to increase the scope and difficulty of problem- or case-based activities they use in their classrooms. Although basic mathematic and com munication skills still are considered essential for students to develop, educators are becoming increasingly aware that curricula must place less emphasize on learning specific factual information and place more on the ability to locate and use information to solve problems and to think criti cally about issues. The reference databases pro vided in support of Activities 2 and 5 and the sim ulation provided for Activity 3 allow teachers to involve students in problem-solving and in locating and using information while also teaching the basic skills students are expected to acquire.

Finally, well-designed instructional software can **increase teacher productivity**. There are a variety of ways such software can accomplish these goals, such as helping teachers with assessment, record keeping, and classroom planning and manage ment. Instructional software such as the CD-ROM enclosed with this module offers teachers the con venience of a full week of instruction that is stored and transported in the space of a single CD and this teacher's guide. Instructional software also can give teachers increased credibility in their students' eyes. Many of today's students have been raised in a technology-rich environment and often respond positively to the use of technology-based methods that streamline and enhance communication between teachers and students and, in so doing, increase the efficiency of both.

Organizing Collaborative Groups

All of the activities in this mod ule are designed to be completed by groups of students working together. Although many of the specific steps can be completed by individual stu dents working alone, this strategy will not stimu late the types of student-student interactions that are one of the goals of active, collaborative, inquiry-based learning. Therefore, we recommend that you organize collaborative groups of between two and six students each, depending on the number of computers equipped with CD-ROM drives you have available. Students in groups larger than this likely will have difficulty organizing the student-computer interactions equitably, which can lead to one or two students assuming the primary respon sibility for the computer-based work. Although this type of arrangement can be efficient, it means that some students do not get the opportunity to experi ence the in-depth discovery and analysis that the enclosed CD-ROM was designed to stimulate.

If you are teaching all five activities as a unit, we recommend that you keep your students in the same collaborative groups for all of the activities. This will allow each group to develop a shared experience with the software and with the ideas and issues that the activities present. A shared expe rience also will enhance your students' perceptions of the activities as a conceptual whole. This will be particularly important in the activities toward the end of the module, as students consider some of the ethical and logistical complexities associated with our growing knowledge about human genetic vari ation.

If your student-to-computer ratio is greater than six students to one computer, you will need to change the way you teach the module from the instructions in the activities. For example, if you have only one computer available, you may want students to complete the CD-based work across an extended time period. You can do this in several ways. The most practical way is to use your computer as a center along with several other centers at which students complete other activities. In this strategy, students would rotate through the computer center, eventually completing the CD-based work that you have assigned.

A second way to structure the activities if you only have one computer available is to use an overhead projection system to display the computer monitor onto a screen for the whole class to see simultane ously. Giving selected students in the class the opportunity to manipulate the program in response to class suggestions and requests can give students some of the same type of autonomy over their learning that they would gain if they were working with the CD in small teams. Some activi ties require students to use the CD for extensive research; if so, give the students printouts of

selected portions of the program to work from. This strategy, however, will not give the students an opportunity to interact personally with the CD. We recommend that you use this strategy only if you have no other options.

Dealing with Values and Controversial Topics

Instructors sometimes feel that the discussion of values is inappropriate in the science classroom or that it "detracts" from the learning of "real" science. The activities in this module, however, are based upon the conviction that there is much to be gained by involving students in analyzing issues of science, technology, and society. Society expects all citizens to participate in the democratic process, and our educational system must provide opportunities for students to learn to deal with contentious issues with civility, objectivity, and fairness. Likewise, students need to learn that science intersects with life in many ways. Opportunities to encounter and consider carefully some of these ways will reinforce and enrich those scientific principles that we desire to teach.

The activities provide a variety of opportunities for students to discuss, interpret, and evaluate basic science and public health issues in the light of values and ethics. Many issues that students will encounter—especially those having to do with individual susceptibility to disease and personal decisions that various people might make about genetic testing and medical treatment—are potentially controversial. How much controversy develops will depend on many factors, such as how similar your students are with respect to socioeconomic status, perspectives, value systems, and religious preferences. It also will depend on how you handle your role as facilitator of the discussion. Your language and attitude may be the factors that influence most the flow of ideas and the quality of exchange among the students.

Neutrality may be the single most important characteristic of a successful discussion facilitator. The following suggestions may help you think about how to guide your students in discussions that balance factual information with values.

- ÄEncourage your students to discover as much information about the issue as possible. Ask questions that help your students distinguish between those components of an idea or issue that scientific research can answer and those components that are a matter of values. Maintaining this distinction is particularly important as students discuss the issues about genetic testing that are raised in Activity 5. Students should understand the importance of accurate information to any discussion and should recognize the importance of distinguishing factual information from opinions.
- ÄKeep the discussion relevant and moving forward by questioning or posing appropriate problems or hypothetical situations. Invite your students to respond to or build on each other's ideas. Avoid asking questions that have exact answers unless the facts are important to the integrity of the discussion. Encourage everyone to contribute, but do not force reluctant students into the discussion.
- ÄEmphasize that everyone must be open to hearing and considering diverse views. Point out that we cannot make intelligent decisions if we close ourselves off from some viewpoints. Even if we cannot agree with or are offended by a viewpoint, we still must hear it so that we know it exists and can consider it as we shape our own views.
- ÄUse unbiased questioning to help the students critically examine all views presented. Help your students consider different points of view thoroughly by asking them to define the relevant arguments and counterarguments. Let the students help you promote the expression of alternative points of view.
- ÄAllow for the discussion of all feelings and opinions. Avoid becoming a censor of views that are radical or shocking (as long as these views are consistent with the facts). When a student seems to be saying something for its shock value, see whether other students recognize the inappropriate comment and invite them to respond.
- ÄAvoid seeking consensus on all issues. This is particularly important in Activity 5. The multifaceted issues that the students discuss result in the presentation of divergent views, and students should learn that this is acceptable.

- ÄKeep your own views out of the discussion. Experts in science education recommend that teachers withhold their personal opinions from students. The position of teacher carries with it an authority that might influence students. The danger also exists that the discussion might slip into indoctrination into a particular value posi tion, rather than an exploration of divergent positions.Either result misses the point of the discussion. If your students ask what you think, you may wish to respond with a statement such as "My personal opinion is not important here. We want to consider your views."
- ÄAcknowledge all contributions in the same even-handed manner. If the class senses that you favor one idea over another, you will inhibit open debate and discussion. For example, avoid prais ing the substance or content of comments. Instead, acknowledge the willingness of stu dents to contribute by making such comments as "Thanks for that idea" or "Thanks for those com ments."As you display an open attitude, a simi larly accepting climate will begin to develop within the class.
- ÄCreate a sense of freedom in the classroom. Remind students, however, that freedom implies the responsibility to exercise that freedom in ways that generate positive results for all. If nec essary,remind them that there is a fine line between freedom and license. In general, free dom is a positive influence, whereas license usu ally generates negative results.
- ÄInsist upon a nonhostile environment in the classroom. Do not allow your students to make ad *hominem* arguments (arguments that attack the person instead of the idea). Help your stu dents learn to respond to ideas instead of to the individuals presenting those ideas.
- ÄRespect silence. Reflective discussions often are slow. If you break the silence, your students may allow you to dominate the discussion.
- ÄFinally, at the end of the discussion, ask your stu dents to summarize the points that they and their classmates have made. Let your students know that your respect for them does not depend on their opinion about any controversial issue. If stu dents feel that they must respond in particular ways to gain your approval, your class will not discuss issues openly and with forthrightness.

Following these general suggestions should help you stimulate meaningful student-to-student interaction with as little direct involvement by you as possible. Initially, some students may have diffi culty responding without specific direction. It is important, however, that you resist the temptation to intervene extensively in the initial, sometimes uncomfortable phase of long silences and faltering responses. Unless students are given opportunities to evaluate ideas and values in the context of a larger problem, they may never learn to do so.

Assessing Student Progress

Because we expect this module to be used in a variety of ways and at a variety of points in an individual teacher's curriculum, we believe the most appropriate mechanism for assessing student learn ing is one that occurs informally at various points within the activities, rather than something that happens more formally, just once at the end of the module. Accordingly, we have integrated a variety of specific assessment components throughout the activities within the module. These "embedded assessment" opportunities include one or more of the following strategies:

- performance-based activities (for example, struc tured discussions of potentially controversial issues);
- presentations to the class (for example, role play ing); and
- written assignments (for example, answering questions or writing magazine or newspaper articles, letters, and short reports).

These strategies allow you to assess a variety of aspects of the learning process, such as students' prior knowledge and current understanding, prob lem-solving and critical-thinking skills, level of understanding of new information, communication skills, and ability to synthesize ideas and apply understanding to a new situation.

An assessment icon and an annotation that describes the aspect of learning you can assess using a particu lar strategy appear in the margin beside the step in which each embedded assessment occurs.

Student Activities

The heart of this module is the set of five activities that follow. These activities are the vehicles that we hope will carry important concepts related to human genetic variation to your students. To review the concepts in detail, refer to Figure 7 in *Implementing the Module*.

As you scan the activities, you will find that each contains several major features.

At a Glance gives you a convenient overview of the activity.

- The **Focus** provides a one-to-two sentence summary of what students do.
- **Major Concepts** state the central idea(s) the activity is designed to convey.

Figure 12 A Möbius strip is a one-sided, one-edged loop. Test this by making a loop with five twists. With a marker, draw a continuous line around the strip, starting at the seam. Your line should pass along "both" sides of the paper before you return to your starting point, even though you do not lift your marker off the paper as you draw. Then run your marker along the edge, again starting at the seam. You should see that the strip also contains only one edge. Loops with odd numbers of twists are Möbius strips; loops with even numbers of twists are not. In this module, we use a five-twist Möbius strip as a metaphor for the relationship between basic science and personal and public health.

- **Objectives** lists three to five specific understandings or abilities students should have after completing the activity.
- **Prerequisite Knowledge** alerts you to the understandings and skills students should have before beginning the activity.
- The **Basic Science-Health Connection** describes how the activity illustrates the relationship between basic science and personal and public health. The mission of the NIH is to "uncover new knowledge that will lead to better health for everyone." This mission statement recognizes that basic science and personal and public health are not separate issues; they are not even two sides of one issue (Figure 12). Rather, they are inextricably linked and form a powerful whole: Research into the basic processes of life leads inevitably to strategies for improving health, and questions about health trigger research into basic processes.

The **Introduction** places the activity in a context and provides a short overview of its key components.

Materials and Preparation provides instructions for collecting and preparing the materials required to complete the activity.

Procedure outlines the activity's steps and provides implementation suggestions and answers to questions. Annotations in the margins, identified by icons, provide specific hints about helping students see connections between basic science and personal and public health (the Möbius strip icon), assessing student understanding (the check mark icon), and focusing students' attention on the activity's major concepts during its closing steps (the "completing-the-puzzle" icon).

Potential Extensions describes ways you can extend or enrich the activity.

All of the **Masters** required to teach the activities are located in a separate section at the end of the module.

Two of the activities (*The Meaning of Genetic Variation* and *Making Decisions in the Face of Uncertainty*) use the enclosed *Human Genetic Variation* CD-ROM. A third activity (*Molecular Medicine Comes of Age*) includes a CD-ROM-based option for teachers who wish to use it. For information about using the CD, see the section "Using the Human Genetic Variation CD-ROM in the Classroom" in *Implementing the Module*. If you do not have enough computers equipped with CD-ROM drives available to conduct these activities with your students, you can use the print-based alternatives. To view and print the instructions and masters for these alternate activities, load the CD onto a computer and click the Print button on the main menu screen. The computer will display a screen showing the resources available for printing from the CD; click on the button labeled Non-CD Lesson Plan from the choices available for the relevant activity. This will reveal the lesson plan and the masters for the alternate, non-CD-based lesson. Click Print again to print these resources.

Figure 13 outlines a plan for preparing for and completing the five activities that follow. The page reference in the caption indicates the pages on which you will find specific preparation instructions. The plan assumes you will teach the activities on consecutive days. If this is not your plan, adjust the timing of your preparation accordingly.

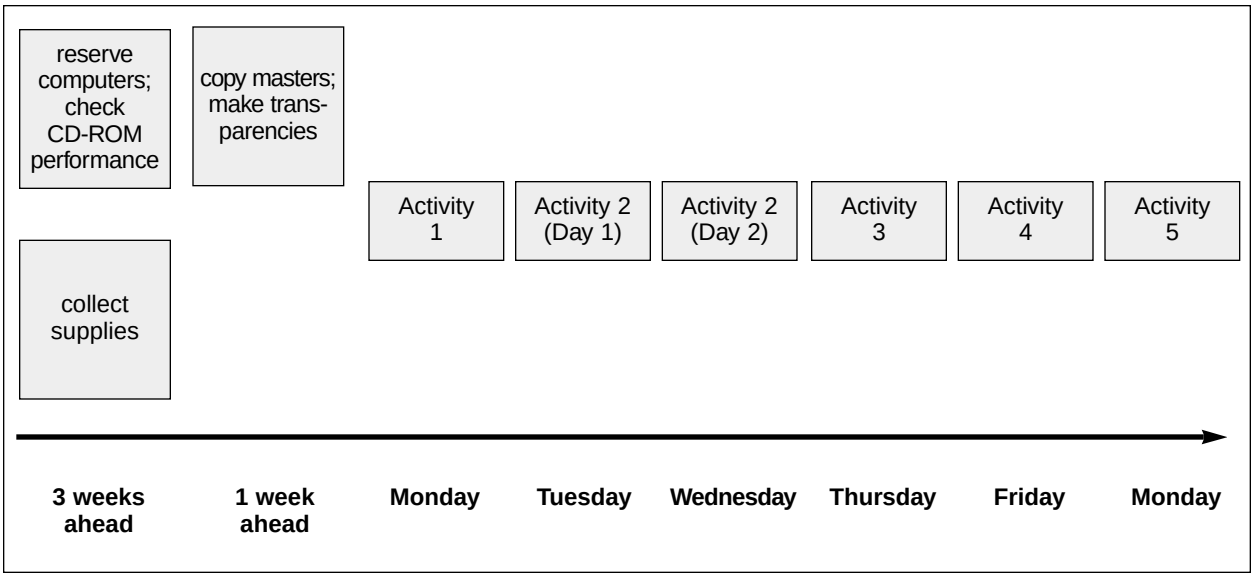


Figure 13 Timeline for teaching the module. Before you begin teaching this module, review this timeline. Instructions for computer set-up are on page 23; those for preparing other required materials are in Materials and Preparation in each activity.

Activity 1
Alike, But Not the Same

At a Glance

Focus: Students conduct a classwide inventory of human traits, construct histograms of the data they collect, and play a brief game that introduces the notion of each individual's uniqueness.

Major Concepts: Humans share many basic characteristics, but there is a wide range of variation in human traits. Most human traits are multifactorial: They are influenced by multiple genes and environmental factors.

Objectives: After completing this activity, students will

- understand that they share many traits;
- understand the extent of genetic similarity and variation among humans;
- be able to explain that most human traits are multifactorial, involving complex interactions of multiple genes and environmental factors; and
- understand that genetic variation can be beneficial, detrimental, or neutral.

Prerequisite Knowledge: Students should be familiar with constructing and interpreting histograms.

Basic Science-Health Connection: This opening activity introduces human variation as a topic that can be systematically studied using the methods of science (for example, gathering and analyzing data). This idea sets the stage for Activity 2, in which students consider the significance of human genetic variation at the molecular level.

Introduction

This activity introduces the module by focusing explicitly on human variation. The primary vehicle is a class inventory of human traits that highlights similarities and differences. Although variation, both phenotypic and genotypic, is the central focus of all five activities in the module, this concept is less explicit in subsequent activities than in this activity.

One goal of the Human Genome Project was to provide the complete sequence of the human genome. Another goal of the genome project is to illuminate the extent of human genetic variation by providing a detailed picture of human similarities and differences at the molecular level. Research indicates that any two individuals are 99.9 percent identical at the level of the DNA. The 0.1 percent where we vary from one another (about 1 out of 1,000 DNA bases) is clearly very important. It is within this small fraction of the genome that we find clues to the molecular basis for the phenotypic differences that distinguish each one of us from all others.

In this activity, students are introduced to the notion that although we are very similar to one another, we also are very different, and our differences reflect a complex interplay between both genetic and environmental factors. This understanding sets the stage for subsequent activities in the module in which students

learn about the molecular differences that help explain our phenotypic differences, and also consider some of the medical and ethical implications of scientists' growing understanding of these differences.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- plant, fish, prepared slide of bacteria
- Master 1.1, *An Inventory of a Few Human Traits* (make 1 copy per student)
- labeled axes on the board or wall in which students can enter data

  Construct four sets of axes on the board or the classroom wall (use masking tape). Label the axes as shown in Figure 14.

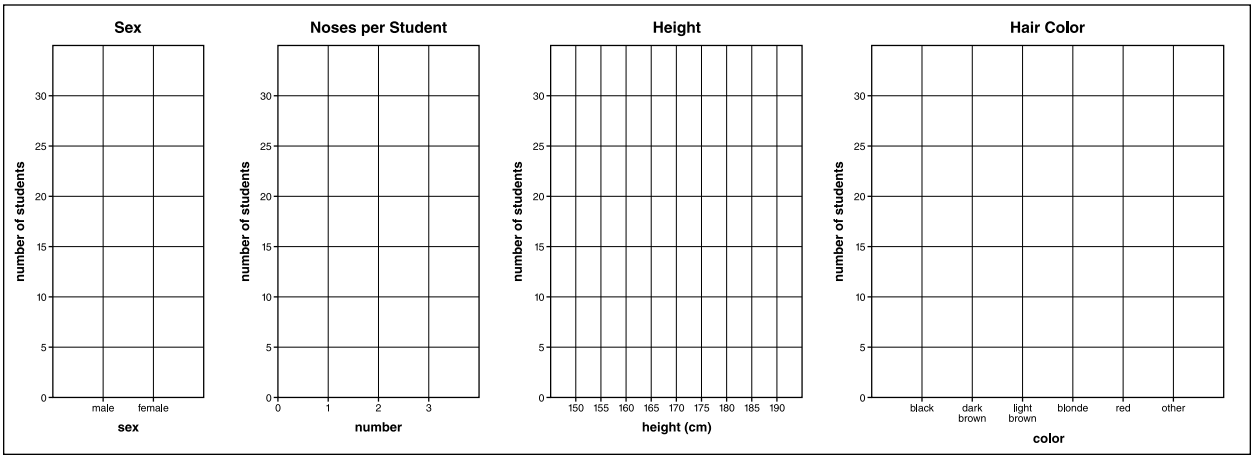
- 120 3 × 5 cards (4 per student; required only if you construct the axes on the wall)
- tape measure (1 per pair of students)
- Master 1.2, *Thinking About Human Variation* (make 1 copy per student)

Procedure

1. **Begin the activity by telling the class something like, "If a visitor from another planet walked into this classroom, he might easily conclude that humans all look very much alike." If students complain that this is not true, answer with something like, "You certainly are more like one another than you are like this plant [point to the plant]. Or this fish [point to the fish]. And for sure, you are more alike than anyone of you is like the bacteria on this slide [wave the prepared slide of bacteria in the air]. Humans—*Homo sapiens*—have a set of traits that define us as a species, just like all other species have a set of traits that define them."**

2. **Continue the activity by saying, "Let's see just how similar you are." Distribute one copy of Master 1.1, *An Inventory of a Few Human Traits*, to each student and ask students to work in pairs to complete them.**

Figure 14 Construct the four sets of axes shown here on the board or on a wall of your classroom.



If students are unfamiliar with the following terms, provide the definitions below.

detached earlobes: Earlobes hang free, forming a distinct lobe.

hitchhiker's thumb: Most distal joint of thumb can form almost a 90 degree angle with the next most proximal joint.

middigital hair: Hair is present on digits distal to knuckles.

cross left thumb over right: Natural tendency is to cross left thumb over right when clasping hands together.

3. **As students complete the inventory, direct their attention to the four sets of labeled axes you prepared. Ask the students to enter their data at the appropriate place on each set of axes.**

   If you constructed the axes on the board, students can use chalk to record their data. If you used masking tape to construct the axes on the wall, ask students to record their data by taping one 3×5 card in the appropriate place on each set of axes.

   Tip from the field test: You may wish to give males one color of chalk or 3×5 card to use in recording their data and give females a different color. This strategy will allow the class to determine if any of the three characteristics other than sex (for example, height) shows differences related to sex.

4. **After the students have finished collecting and recording their data, ask them to look at the four histograms they built and identify what evidence they see in those data that they share many traits with other members of their class.**

   Students may answer that all people have only one nose, and all people are only one sex or the other.

5. **Continue the activity by saying, "But now that I look around the room, it is clear that you *are* different. What evidence do you see in these data that people are different?"**

   Students should recognize that not everyone is the same height and not everyone has the same hair color.

   As students look at the data, you may wish to ask them to compare the shapes of the histograms for sex and height. The sex histogram has two distinct peaks because there are only two categories of individuals—female and male. That is, sex is a discontinuous trait. In contrast, height is a continuous trait that has many categories of individuals, ranging from very short to very tall. The shape of the height histogram may begin to approach a bell curve, or normal distribution. It may also have two peaks—a bimodal distribution—with one peak representing the female students and the other peak representing the male students.

6. **Challenge the students to try to describe just how different they are by**

guessing how many traits they would have to consider to identify any given student in the room as unique. Write the students' predictions on the board.

7. **Conduct the game described below with several volunteers.**
   - **Choose a volunteer to determine his or her "uniqueness" as compared with the other students.**
   - **Ask all of the students to stand.**
   - **Invite the volunteer to begin to identify his or her phenotype for each of the 13 human traits listed on *An Inventory of a Few Human Traits.* Begin with the first trait and proceed sequentially. As the volunteer lists his or her phenotype for each trait, direct the students who share the volunteer's phenotype for that trait to remain standing. Direct all other students to sit.**
   - **Continue in this fashion until the volunteer is the only person still standing. Count how many traits the class had to consider to distinguish the volunteer from all other students in the class. Compare this number with the students' predictions.**
   - **Repeat as desired with another volunteer.**
8. **Ask students to work in pairs to answer the questions on Master 1.2, *Thinking About Human Variation.***

Collect and review the students' completed worksheets to assess their understanding of the activity's major concepts.

Question 1 Some human traits can be changed by human intervention and some cannot. Provide examples of each of these types of traits.

Biological sex and blood type cannot be changed. Hair color, skin color, and even height and mental abilities can be changed by human intervention. Students also may suggest that body piercing alters human traits.

Increasing evidence indicates that all human diseases have genetic and environmental components. Point out that diseases such as cancer, heart disease, and diabetes as traits that show an interaction between genetic and environmental factors. Students will consider this concept in Activity 4, *Are You Susceptible?*

Question 2 You probably already know that some traits are genetic and others are environmental. But most human traits reflect an interaction between genetic and environmental factors. Name some traits that might fall into this category and explain why you think they do.

Height, weight, intelligence, and artistic or athletic ability are examples of traits that are influenced by genetic and environmental factors. Some students may mention disorders such as certain types of cancer or even psychiatric disorders. We know that these types of traits are both genetic and environmental because we see evidence that they run in families and because we know we can modify them by changing the environment.

Question 3 Describe some of the benefits of human genetic variation. What are some of the potential problems that it can cause?

Students may mention a number of benefits, such as allowing people to be distinguished from one another and increasing the diversity of abilities, interests, and perspectives among humans. Some students may recognize that genetic variation also benefits the species because it is the basis for evolution by natural selection. Students will consider this aspect of variation in Activity 2, *The Meaning of Genetic Variation*.

Expect students to recognize that just as being different from one another has advantages, it also has disadvantages. For example, genetic variation makes successful tissue and organ transplants more difficult to accomplish than if we were all genetically identical. Students also may note that the existence of real (or perceived) differences among members of a population can allow prejudice and discrimination to exist.

You may wish to point out that research reveals that more variation exists within populations than between them (Figure 15). As noted in *Understanding Human Genetic Variation*, an examination of human proteins demonstrated that about 90 percent of all variation occurred within populations, whereas only 10 percent occurred between populations. That is, we are more "like" people with other ethnic or geographic origins than we might think.

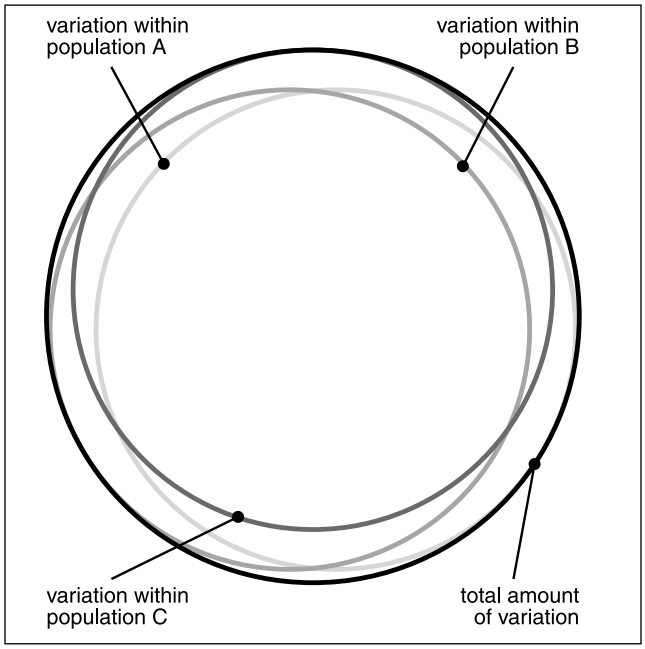


Figure 15 Most variation occurs within populations. A Venn diagram is a useful way to illustrate this idea to students. Note that the amount of genetic information that different populations have in common (areas where circles overlap) is much greater than the amount that is unique (areas where there is no overlap).

These open-ended questions invite students to step back from the activity's details to consider its broader implications. Another way to invite such reflection is to ask students to identify the most important or the most interesting idea they learned as a result of completing the activity.

9. Invite students to summarize the activity's major concepts by asking, "What has this activity illustrated about how one human compares with another human? What has it illustrated about human variation in general?"

Expect students to recognize that humans share many traits. Students also may note that there is a wide range of variation in human traits and one does not have to consider very many traits before a given person's uniqueness is demonstrated. Students should point out that some traits can be changed by human intervention and some cannot, and that although some traits are genetic and others are environmental, most human traits reflect an interaction between genetic and environmental factors (that is, most are multifactorial). You may wish to introduce the term "multifactorial" at this point; students will study multifactorial traits in more detail in Activity 4, *Are You Susceptible?*

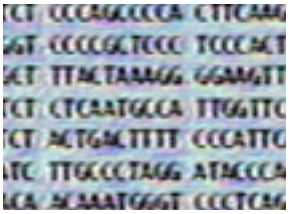
Be sure that students generalize their responses to focus on variation in populations, not variation simply between themselves and their partners. Point out that the concept of variation in populations will reappear in different, but less obvious, ways in the other activities in this module.

Potential Extensions

This activity introduces students to several ideas that you may wish them to explore in more depth. For example, assign students to use their textbooks to identify the biological mechanisms that lead to and maintain diversity in populations.

Alternatively, ask students to list some of the advantages and disadvantages of genetic variation in nonhuman populations. Invite them to locate and report on cases where scientists are concerned that it may be diminishing (for example, in domesticated crops and in populations of endangered species being maintained in zoos and other protected settings).

Finally, to extend the discussion of the multifactorial nature of most human traits, challenge students to suggest ways that scientists might investigate the relative contributions that heredity and the environment make to such traits (for example, twin studies or studies of adopted children in relation to their adoptive and biologic parents).



Activity 2

The Meaning of Genetic Variation

At a Glance

Focus: Students investigate variation in the *beta globin* gene by identifying base changes that do and do not alter function, and by using several CD-ROM-based resources to consider the significance in different environments of the base change associated with sickle cell disease.

Major Concepts: The ultimate source of genetic variation is differences in DNA sequences. Most of those genetic differences do not affect how individuals function. Some genetic variation, however, is associated with disease, and some improves the ability of the species to survive changes in the environment. Genetic variation, therefore, is the basis for evolution by natural selection.

Objectives: After completing this activity, students will

- recognize that the extent of molecular variation between two people is only about 0.1 percent, but because of the large size of the human genome, this translates to about 3 million base differences;
- understand that most human genetic variation does not affect function;
- be able to explain that some human genetic variation is related to disease and provide an example; and
- be able to describe a benefit of human genetic variation and relate this benefit to human evolution by natural selection.

Prerequisite Knowledge: Students should understand basic Mendelian patterns of inheritance, especially autosomal recessive inheritance; the basic structure of DNA; the transcription of DNA to messenger RNA; and the translation of messenger RNA to protein.

Basic Science-Health Connection: Although the idea is made explicit only in annotations to teachers, this activity illustrates how advances in science and technology have allowed us to establish relationships between some genetic variations and particular phenotypes. For example, our understanding of the relationship between DNA and protein has allowed us to establish a relationship between a change in a single base pair and the symptomology of sickle cell disease. Similarly, our understanding of the basic biochemical mechanisms underlying the symptoms associated with sickle cell disease has provided important clues about possible strategies for clinical intervention. You may wish to make some of these points with your students as they complete the activity.

Introduction

As discussed in *Understanding Human Genetic Variation*, there is considerable variation between the genomes of any two individuals, but only a small amount of that variation has any significant biological impact, that is, produces differences in function. The Human Genome Project will continue to illuminate

the extent of human genetic variation as well as the variations that have biological significance.

This activity uses an examination of variation in a 1,691-base segment of the *beta globin* gene to help students consider the extent of human genetic variation at the molecular level and the relationships between genetic variation and disease and between genetic variation and evolution.

Materials and Preparation

You will need to prepare the following materials before conducting this activity*:

- Master 2.1, *How Much Variation? Beta Globin Gene—Person A* (make 1 copy per student)
- Master 2.2, *How Much Variation? Beta Globin Gene—Person B* (make 1 copy per student)
- Master 2.3, *How Much Variation? Doing the Math* (make 1 copy per student)
- Master 2.4, *Exploring Sickle Cell Disease* (make 1 copy per student)
- Master 2.5, *Results of the Lindsey Test* (make 1 copy per team)
- *Human Genetic Variation* CD-ROM (1 per team)

*Day 1, Step 12 describes an optional laboratory exercise that you may wish to conduct to enrich your students' understanding of molecular variation and the methods by which it can be identified and studied. Information about the materials required is provided on page 42.

Follow the instructions on page 23 to load the CD-ROMs on the computers the students will use.

Note to teachers: If you do not have enough computers equipped with CD-ROM drives to conduct this activity, you can use the print-based alternative. To view and print the instructions and masters for this alternate activity, load the CD onto a computer and click the Print button on the main menu screen. The computer will display a screen showing the resources available for printing from the CD; click on the button labeled Non-CD Lesson Plan from the choices available for Activity 2, *The Meaning of Genetic Variation*. This will reveal the lesson plan and the masters for the alternate, non-CD-based lesson. Click Print again to print these resources.

Procedure

DAY 1

1. **Introduce the activity by asking students to identify the ultimate source of the variation they investigated in Activity 1.**

   Students should recognize that the ultimate source of genetic variation is differences in DNA sequences.

2. **Explain that in this activity, students will investigate human genetic variation at a molecular level and examine the impact of that variation on biological function. Distribute one copy of Masters 2.1, *How Much Variation? Beta Globin Gene—Person A,* and 2.2, *How Much Variation?***

***Beta Globin Gene—Person B,* to each student. Explain that the sequences on these pages come from the *beta globin* gene in two different people.**

Hemoglobin, the oxygen carrier in blood, is composed of four polypeptide chains, two alpha polypeptide chains and two beta polypeptide chains. The *beta globin* gene encodes the amino acid sequence for the beta chain. *Person A* and *Person B* each show 1,691 nucleotides from the "sense" strand of the gene (that is, the strand that does not serve as the template for transcription and thus has the same base sequence as the messenger RNA, with Ts substituted for Us). Both the sense strand of DNA and the messenger RNA are complementary to the DNA strand that serves as the template for transcription. We recommend that you remind students that DNA is double-stranded, even though only one strand is shown here. Explain that geneticists use "short cuts" like this because, given the sequence of one DNA strand, they can infer the sequence of the complementary strand.

The *beta globin* gene is one of the smallest human genes that encodes a protein; the entire gene has only about 1,700 nucleotide pairs and includes just two introns. The sequences on *Beta Globin Gene—Person A* and *Beta Globin Gene—Person B* do not show the gene's promoter regions, but begin with the first sequences that are translated.

3. **Ask the students to read the information at the top of each page and then estimate the total number of bases on each page. Direct students to write their estimate at the top of the page.**

   The total number of bases on *each* page is 1,691. Students will need this number to complete their calculations in Step 6.

4. **Remind the students that the sequences on the masters come from the *beta globin* gene in two different people. Ask the students what they notice when they compare the sequence from person A with the sequence from person B.**

   Students should notice that most of the sequence appears to be exactly the same in both people. They also should notice that the bases that are in bold are different. If necessary, point out that these bases are at the same positions in each gene (that is, be sure that students realize that only these two bases, located in these specific positions, are different in the sequences from person A and person B).

5. **Point out that this sequence is only 1,691 bases long and the complete human genome is approximately 3 billion bases long. Ask the students how they might use the sequences for person A and person B and the total size of the human genome to estimate the extent of variation (the number of bases that differ) between person A and person B. Ask as well what assumption they would be making as they arrived at their estimate.**

Students could estimate the extent of variation across the entire genome by calculating the percentage of difference between the two sequences shown for person A and person B, and then multiplying this percentage by 3 billion (the approximate number of bases in the human genome). This estimate assumes that the sequence shown displays a typical amount of variation.

6. **Distribute one copy of Master 2.3, *How Much Variation? Doing the Math,* to each student and direct the students to use the master as a guide to estimate this value.**

   If your students need help completing this estimate, suggest that they first try the example at the bottom of the master.

   The proportion of sequence difference between person A and person B is 2 / 1,691 = .001 (rounded off). To make this more concrete for your students, note that this means that about 1 base in every 1,000 is different. The percentage difference is $.001 \times 100 = 0.1$ percent.

   The total number of base differences would be $3{,}000{,}000{,}000 \times .001 = 3{,}000{,}000$ or, in scientific notation, $3 \times 10^9 \times 10^{-3} = 3 \times 10^6$. That is, we could expect to find 3 million base differences in DNA sequence between any two people.

   Note that the actual number of base differences between two people likely is somewhat higher than this because this estimate, based as it is on the approximate size of the human *genome* (one copy of each of the autosomes, plus the X, Y, and mitochondrial chromosome), does not take into consideration the fact that humans are diploid.

7. **Ask students what their estimates indicate about the extent of human genetic variation at the molecular level.**

   Students should recognize that at the molecular level, humans are far more alike (about 99.9 percent of the bases are the same) than they are different (only about 0.1 percent of the bases are different). Students also should realize, however, that even a small percentage difference can represent a very large actual number of differences in something as large as the human genome.

   If students have difficulty reaching these conclusions, help them by asking questions such as, "Based on this comparison, do you think that at the molecular level, people are more alike than they are different or vice versa?" and "How can a difference of only 0.1 percent (1 in 1,000) result in such a large number of differences (3 million differences)?"

8. **Explain that the rest of the activity focuses on this 0.1 percent difference between people. Ask students questions such as "Do you think these differences matter? What effect do you think they have? What might affect how much a specific difference matters?"**

These questions focus students' attention on the *significance* of the differences, instead of the *number* of differences. Remind students of the differences among people that they observed in Activity 1 and point out that most of these differences have their basis in a difference in the DNA sequence of particular genes (probably pierced versus non pierced body parts do not). To help them understand the magnitude of the number of differences between their DNA and that of another person, ask students if they think there are 3 *million* differences in appearance and biological functions between themselves and the person sitting next to them.

9. **Explain that studying the *beta globin* gene more closely will help students begin to answer these questions for themselves. Direct students to examine the sequences on *Beta Globin Gene—Person A* and *Beta Globin Gene—Person B* again. Explain that the regions that show bases grouped in triplets are from the coding regions ("exons") of the gene, while the other regions are from the noncoding regions ("introns"). Then ask students which of the two base differences in bold is most likely to matter, and why.**

   Most eukaryotic genes are composed of both coding and noncoding regions, which are transcribed into an initial messenger RNA. The noncoding introns are then spliced out of the RNA; other processing steps ultimately result in the mature messenger RNA that is translated into protein. Students should realize that the second base difference occurs in a noncoding region of the gene and is unlikely to have an impact on individuals. The first difference occurs in a coding region and is more likely to matter.

10. **Explain that although 3 million base differences sounds like a lot, most of these differences have no significant impact on individuals, either because they occur in a noncoding region or for another reason. Point out that most of these 3 million differences can only be detected by examining the DNA sequence.**

A major concept that students should understand from Day 1 of the activity is that most genetic differences do not affect how individuals function.

   Students should now understand that while some base differences occur in coding regions and may result in an altered amino acid sequence in the protein coded for by a gene, others occur in noncoding regions where they likely have no impact. Point out that only a small percentage of the DNA sequences in the human genome are coding sequences. Furthermore, only a small percentage of the noncoding DNA sequences are regulatory sequences such as promoters or enhancers that can influence the amount of gene product that results from a given gene. The remaining DNA sequences (the majority of the total DNA sequences in the genome) have no known function. Most of the variations in DNA sequence occur in these latter sequences and have no detectable impact.*

   If you wish to offer your students a more sophisticated understanding of why most DNA sequence differences have no impact, extend

the discussion to include the following ideas. Even many of the differences that occur in coding regions have no impact. Only those differences that result in a change in amino acid sequence in a critical region of the protein (one that affects the function of the protein), or that result in a premature stop codon in the RNA (and thus a truncated protein) have a significant impact on the individual carrying that variation. As students will see in Day 2, those few differences that do affect individuals often have devastating consequences.

*You may wish to clarify for students the reason that most molecular variation occurs in noncoding regions. It is true that there are more noncoding than coding regions. However, the fundamental biological reason for the increased variability of noncoding regions is that there is no selective pressure exerted on changes in these silent / nonfunctional regions. You also may wish to point out that some differences that occur in noncoding regions do have an impact. For example, several mutations within introns in the *beta globin* gene cause incorrect splicing of the messenger RNA and, as a result, several codons may be inserted into or omitted from the sequence, leading to nonfunctional beta globin polypeptides.

11. **Point out the codon in which the first difference between the two sequences occurs and tell students that person A has normal hemoglobin, while Person B has an abnormal hemoglobin that is associated with sickle cell disease. Explain that the single base difference in this codon determines whether a person has normal hemoglobin or sickle hemoglobin.**

    If you wish to take the time, ask students to identify the actual amino acid difference between these two types of hemoglobin, based on the difference in the DNA sequence of the codon you identified. This is an opportunity for students to review the translation process and the genetic code. Remind them that the sequence they have is the same as the messenger RNA sequence, except it has Ts where the RNA would have Us. Normal hemoglobin has glutamic acid (RNA codon GAG) in the position where sickle cell hemoglobin has valine (RNA codon GUG).

12. **Tell students that in the next part of the activity, they will consider the consequences of the genetic variation that results in sickle cell disease. Distribute Master 2.4, *Exploring Sickle Cell Disease,* and direct students to organize into their teams, view the mini documentary *What Is Sickle Cell Disease?* on the *Human Genetic Variation* CD-ROM, and begin working on the questions.**

    Give the students about 30 minutes to complete their research. Notice that most of the information they need is located in the *Reference Database* on the CD-ROM. If the students' textbooks have an adequate description of sickle cell disease, you may wish to assign certain questions on *Exploring Sickle Cell Disease* for them to complete at home.

When students reach Question 2 on the master, they should explain how they intend to test the Lindsey twins. Give the team a copy of the test results (Master 2.5, *Results of the Lindsey Test*) after the students correctly explain the test they would have conducted.

Instead of giving students the results of the test they propose in Question 2 on *Exploring Sickle Cell Disease*, you may want them to complete the relevant laboratory themselves. Kits such as Ward's *Identification of Genetic Diseases* laboratory activity (catalog # 36WS374) are available that you can adapt to this purpose. If you plan to have your students complete the lab, schedule an additional one-half to one class period for the activity.

DAY 2

1. **Open the second half of the activity by directing students to meet in their teams to complete or review their answers to the questions on *Exploring Sickle Cell Disease.* After they have completed their work, convene a class discussion in which you invite students to share their answers to the questions.**

   Question 1a What are the primary symptoms of sickle cell disease? What happens in a person's body to cause these symptoms?

   People with sickle cell disease periodically experience symptoms that include severe pain and fever. The symptoms occur when the sickle hemoglobin (Hb S) inside red blood cells forms long crystals under conditions of low oxygen concentration. The red blood cells elongate and assume a "sickle" shape. The crystallized hemoglobin damages the cell membranes, causing them to burst easily. The misshapen cells also clog blood vessels. The result is the destruction of many red blood cells within a few hours and a disruption of oxygen transport that can lead to death.

   Question 1b How is Hb S (sickle hemoglobin) different from Hb A (normal hemoglobin)?

   Sickle hemoglobin (Hb S) has the amino acid valine in the position where normal hemoglobin (Hb A) has the amino acid glutamic acid.

   Question 1c How can this difference in hemoglobin be detected in the laboratory?

   Because of the difference in the amino acid sequence of Hb A and Hb S, the two forms of hemoglobin have different charges. The two forms can be separated using electrophoresis because Hb S moves more slowly in an electric field than Hb A.

   Question 1d What does this difference in hemoglobin tell you about the DNA of people whose cells make Hb S as compared with people whose cells make normal hemoglobin?

The sequence of DNA that codes for hemoglobin in people whose cells make Hb S must be different from the sequence of DNA that codes for hemoglobin in people whose cells make Hb A. The allele that codes for Hb A has the nucleotide A at a place where the allele that codes for Hb S has the nucleotide T.

Question 1e What is the difference between sickle cell disease and sickle cell trait? Demonstrate in your answer that you understand how sickle cell disease is inherited.

People who have sickle cell disease have inherited two alleles for sickle cell hemoglobin, one from each of their parents. They are homozygous for the sickle cell hemoglobin allele. People who have sickle cell trait have inherited one allele for sickle cell hemoglobin from one parent and one allele for normal hemoglobin from the other parent. They are heterozygous and usually have no symptoms.

Highlight the contribution of basic science to the improvement of personal and public health by asking your students whether an early-20th-century physician would have answered Ms. Lindsey's question in this manner. The answer, of course, is no. The first observation of sickle-shaped cells was made in 1910, but the molecular basis of the disease was not worked out until 1949. You may also note that direct diagnosis of this disease through DNA analysis of a person's genotype was made possible in the mid-1980s.

Question 2 Use what you learned about sickle cell disease and trait to propose a way to determine whether Ms. Lindsey's twins have sickle cell trait. Explain your procedure to your teacher, then use the information provided on the handout your teacher will give you to determine the results of the test.

Students should explain the following procedure: Collect hemoglobin from Jason and from Sondra and determine the form(s) of hemoglobin each has using gel electrophoresis. "Standards," or controls, of normal and sickle hemoglobin should be included for comparison.

If a twin is normal, his or her hemoglobin will migrate on the gel in parallel with the Hb A standard. If a twin has sickle cell disease, his or her hemoglobin will migrate like the Hb S standard. If a twin is heterozygous (has sickle cell trait), his or her hemoglobin will contain two forms of hemoglobin, one that migrates like Hb A and one that migrates like Hb S.

Question 3 Write the dialogue for a brief (2–3 minute) scene in which you explain to Ms. Lindsey the results of the tests you ran on the twins, what these results say about the inheritance of the sickle cell trait in her family, and the implications of your findings for the twins' health.

Responses will vary, but students should indicate that Sondra has sickle cell trait and Jason has sickle cell disease. These results indicate that both Ms. Lindsey and her late husband also have/had sickle cell trait; that is, they are both heterozygous for the sickle cell allele and the normal allele, because neither of them are/were ill, but each of them must have given a sickle cell allele to Jason. Sondra should be fine, but Jason has sickle cell disease.

Collect the students' written scenes or have each team perform its scene for the class as a way to assess students' understanding of the inheritance of sickle cell disease.

2. **Ask students what their study of the *beta globin* gene and sickle cell disease has illustrated about human genetic variation.**

   Students should be able to describe the extent of genetic variation from one person to another and should be able to explain that most of these differences do not have a significant biological impact. Students should recognize, however, that some variation (for example, the single base change associated with sickle cell disease) produces negative consequences.

3. **Summarize the students' answers by saying, "So you are saying that most variation does not make a difference and that some variation is negative. Is it possible that some variation also is positive?" Entertain several answers to this question.**

   Most students will recognize that it is possible that some variation is positive.

4. **Ask students, as a final challenge, to imagine that they are doctors practicing in Cameroon, in west-central Africa. Direct them to return to the resources on the CD-ROM to compare the incidence of sickle cell disease in Cameroon with its incidence in the United States and to determine how scientists explain the difference.**

   The incidence of sickle cell disease among black Africans is as much as 16 times higher than the incidence among African Americans (4 percent compared with .25 percent). Scientists believe this difference is related to the occurrence of malaria in many parts of Africa. People who are homozygous for the normal allele for hemoglobin die of malaria more often than people who are heterozygous for the normal allele and the sickle allele for hemoglobin. Thus, more heterozygotes live than people who are homozygous for the normal allele, and they pass their allele for sickle hemoglobin on to many of their children. The result is that the proportion of this allele is higher in the population than it would be if there were no threat of malaria. In contrast, in the United States where there is practically no threat of malaria, people with sickle cell trait (heterozygotes) are no more likely to live than those who are homozygous for the normal allele for hemoglobin. So the proportion of the allele for sickle hemoglobin remains at a very low level in the population because those individuals who inherit two copies of this allele suffer with sickle cell disease and frequently die before passing their alleles on to any offspring.

5. **Ask students how this information would change what they would say to Ms. Lindsey.**

   The only thing that would change is the implication of the findings for the twins' health. Jason will still have sickle cell disease, but Sondra should have enhanced resistance to malaria.

6. Close the activity by challenging the class to answer the following questions:

- **Will natural selection favor the survival of people who produce Hb S or people who produce normal hemoglobin?**

  The critical variable here is the environment in which the Hb S variation is expressed. In environments where malaria is endemic, those who are heterozygous for the Hb S allele (HbA / Hb S) will be more resistant to malaria than are those who are homozygous for the Hb A allele (Hb A / Hb A). Evidence indicates that natural selection has favored the heterozygous state in those environments, therefore maintaining the Hb S allele in relatively high frequencies in some populations during the course of human evolution. In a nonmalarial environment, there is no known selective advantage to carrying the Hb S allele in the heterozygous state. Those who are homozygous for the Hb S allele (Hb S / Hb S) likely will experience the symptoms of sickle cell disease in any environment.

This challenge will reinforce a major concept of this activity. Some genetic variation has negative consequences for individuals. However, some genetic variation improves the ability of the species to survive changes in the environment. Genetic variation is the basis for evolution by natural selection.

- **All populations have genetic variations that lead to increased incidence of particular disorders (for example, cystic fibrosis among Caucasians of European ancestry, Tay-Sachs disease among Eastern-European Jews, and a particular type of thalassemia—a blood disorder—among Asians). Challenge students to explain why such apparently harmful variations have been maintained in those populations.**

  Although most genetic variation is meaningless, some of it is harmful and some of it is beneficial because it improves the ability of the species to survive changes in the environment. The most likely explanation for these examples is the one that has been most clearly established for sickle cell disease: There is a survival / reproductive advantage for people who are heterozygous as compared with those who are homozygous for the normal allele.

  In the case of cystic fibrosis, there is good evidence that those who carry one CFTR allele associated with the disease have increased resistance to typhus, a common killer in Europe in past centuries. There also is circumstantial evidence that those who have one allele associated with Tay-Sachs disease may be more resistant to tuberculosis than those who are homozygous for the normal allele.

Activity 3

Molecular Medicine Comes of Age

At a Glance

Focus: Students discover some of the benefits of understanding human genetic variation at the molecular level by assuming the roles of employees of two fictional pharmaceutical companies to solve problems related to the development of new drugs.

Major Concepts: One of the benefits of understanding human genetic variation at a molecular level is its practical value for helping us understand and treat disease. The development of effective gene-based therapies is an exciting outcome of human genetic research. These therapies, however, are potentially many years away for many diseases.

Objectives: After completing this activity, students will

- appreciate that identifying and sequencing disease-related genes helps scientists better understand and treat disease;
- be able to explain that our increasing understanding of how genetic differences among people affect response to drug treatment will change how physicians prescribe drugs in the future;
- be able to explain how understanding the molecular structure of a disease-related gene can help scientists develop new strategies for treating the disease; and
- recognize that as our understanding of human genetic variation improves, we likely will see many changes in how physicians diagnose and treat human diseases.

Prerequisite Knowledge: Students should understand the relationship among DNA, RNA, protein, and amino acids as well as how to interpret data displayed in tables.

Basic Science-Health Connection: This activity highlights the contribution that scientists studying human genetic variation at the molecular level are making to modern medicine. Research in genetics has made many contributions to clinical medicine across the last century. Research associated with the Human Genome Project is significantly changing not only how we think about human disease, but how we treat it.

Introduction

Activity 3, *Molecular Medicine Comes of Age*, and Activity 4, *Are You Susceptible?*, focus students' attention on the practical, medical applications of understanding human genetic variation at a molecular level.

Activity 3 uses two vehicles—variable responses to drugs and the development of treatment strategies targeted at a disease's biochemical mechanism—to highlight some of the ways scientists can use molecular information to improve disease treatment. That is, Activity 3 focuses on those portions of Figure 6 that deal with pharmacogenomics and targeted drug therapy. An extension to Activity 3 invites students to consider gene therapy as another strategy made possible by a knowledge of molecular genetics.

Geneticists long have known that there is individual variation in the response to certain drugs. For example, in the early part of the 20th century, both Archibald Garrod and J.B.S. Haldane suggested that biochemical individuality as a function of genetic variation might explain people's unusual reactions to drugs and food. By the middle of the 20th century, biologists had identified several clear associations between certain genotypes and adverse drug reactions, including adverse reactions by some people to the drug succinylcholine, which is used as a muscle relaxant during surgery. If treated with this drug, individuals who produce a variant of the enzyme pseudocholinesterase, which normally metabolizes the drug, are in danger of extended depression of respiratory muscles and can suffer prolonged periods of apnea (cessation of breathing), which can be fatal. This is but one example of adverse drug reactions; a study reported in the 15 April 1998 issue of the *Journal of the American Medical Association* found that as many as 106,000 hospitalized patients per year had *fatal* adverse reactions to drugs. This would rank such reactions between the fourth and sixth leading causes of death in the United States.

Biologists also have long known that understanding the molecular structure of a disease-related gene can help them identify potential targets for intervention. As described in *Understanding Human Genetic Variation*, a striking example of this approach to combating disease is recent work on cystic fibrosis. Cystic fibrosis is the most common fatal genetic disease in the United States, affecting approximately 30,000 people. Currently, about half of those affected die by age 30. Since the identification in 1989 of the gene that is altered in cystic fibrosis, the pace of basic research has increased rapidly, and scientists are optimistic that they will be able to translate new knowledge about the molecular basis of the disease to new strategies to improve patients' lives.

In this activity, students assume the roles of employees of two fictional pharmaceutical companies. Each company, Firm A and Firm B, is facing a significant challenge related to the development of a new drug. Firm A is developing a drug to treat asthma. Unfortunately, preliminary test results show variable and unpredictable effects. Student working as employees of Firm A must discover an explanation for these results and recommend a course of action. As students investigate this problem, they learn about the relationship between genetic variation and individual responses to drugs, and discover one way in which pharmaceutical companies are beginning to deal with this issue.

In contrast, Firm B wants to develop a new drug to treat cystic fibrosis. Students working as employees of Firm B discover first that most current treatments for this disease address its symptoms and not its cause. Students are then challenged to identify as many points as possible at which the biochemical processes underlying this disease could be corrected.

As students investigate this problem, they learn that knowing the sequence of a disease-related gene and understanding the disease's biochemical basis can help scientists develop exciting new approaches to treatment.

Because the benefits expected from both pharmacogenomics and targeted drug therapy are still largely unrealized, this activity is a bit futuristic and you may

wish to acknowledge this to students. It is clear, however, that the era of molecular medicine—the application of knowledge about the molecular basis of variation to treating human disease—already is upon us. Although molecular medicine is just beginning to develop, the field has enormous potential for the improvement of personal and public health.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- Master 3.1, *Molecular Medicine Comes of Age* (make 1 overhead transparency)
- Masters 3.2–3.5, *Saving Firm A* (make 1 copy of each master for each team that will complete this part of the activity)
- Master 3.6, *Report Form for Firm A* (make 1 copy per student who will complete this part of the activity and 1 overhead transparency)
- Master 3.7, *Some New Genetic Data (Firm A)* (make 1 copy per team)
- Masters 3.8–3.11, *Saving Firm B* (make 1 copy of each master for each team that will complete this part of the activity)
- Master 3.12, *Report Form for Firm B* (make 1 copy per student who will complete this part of the activity and 1 overhead transparency)
- Master 3.13, *Some New Information (Firm B)* (make 1 copy per team)

Procedure

1. **Introduce the activity by displaying a transparency made from Master 3.1, *Molecular Medicine Comes of Age,* and asking students what they think the statement means and whether they can think of any specific examples that illustrate or provide evidence for this point.**

   Students should be able to explain that understanding human genetic variation at a molecular level means identifying the specific differences in base sequence that distinguish one human from another. Although students likely will not mention pharmacogenomics and targeted drug therapy as examples of health care strategies that depend on understanding molecular variation, they may mention gene therapy as a strategy.

   Students may have difficulty expressing these ideas in their own words. You may wish to help them by asking probing questions such as "What does it mean to understand human genetic variation at a molecular level?" and "Can you think of any way in which finding and sequencing the gene related to a disease could help scientists develop ways to treat it?"

Asking students to explain the phrase "understand human genetic variation at a molecular level" will help you assess what they learned from the first part of Activity 2.

2. **Explain that the students' challenge in this activity is to investigate two examples that illustrate and provide evidence for this point. Explain further that students will investigate these examples by acting as teams of employees in two pharmaceutical companies that are facing problems that threaten the companies' futures.**

3. **Divide the class in half and explain that one half of the class will act as employees in Firm A and the other half will act as employees in Firm B. Tell**

students that the problems the two firms face are different, but both problems can be solved in ways that relate to the statement on the transparency.

4. **Direct students to organize into their teams. Distribute one copy each of Masters 3.2, 3.3, 3.4, and 3.5, *Saving Firm A, [Role],* to each team in one half of the class and one copy each of Masters 3.8, 3.9, 3.10, and 3.11, *Saving Firm B, [Role],* to each team in the other half. Also distribute one copy of Master 3.6, *Report Form for Firm A*, or Master 3.12, *Report Form for Firm B,* to each student and explain that the students should use these forms to organize their discussions and to report the results of their work.**

   As an alternative to using the masters provided for Firm A, you can have students use the equivalent videos on the *Human Genetic Variation* CD-ROM. Follow the instructions on page 23 to load the CD-ROMs onto the computers students will use.

5. **Instruct the students to decide in their teams who will assume each of the four roles associated with their problem and to distribute the masters accordingly.**

6. **Give the teams 30 minutes to complete their reports and to be ready to defend their analysis of their company's problem and their suggested solution to the class, using the appropriate *Report Form* to organize their thoughts.**

   When students reach Step 6 on the *Report Form* (Master 3.6 or Master 3.12), they will ask you, as vice president for the company, for additional data (Master 3.7, *Some New Genetic Data,* or Master 3.13, *Some New Information*). You can give the teams copies of the masters or you can simulate some mechanism that requires students to search for these data.

   If students use the videos on the *Human Genetic Variation* CD-ROM instead of the masters provided for Firm A, they will need to view the video *Some New Genetic Data* when they reach Step 6. Access to the video is password protected. You will need to give students the password: **gene**.

An interesting way to assess students' understanding of this information is to ask one team to offer an answer to a question, and then ask a different team to evaluate the answer's accuracy and completeness and propose corrections or additions as necessary. This technique helps students learn to offer feedback in a positive way and extends accountability for acceptable answers to more students than simply the team members who provide the initial answer.

7. **After the designated time, call the class to order. Explain that you will assume the role of the vice president for research for Firm A first and then the role of the vice president for research for Firm B, and that you are calling everyone together to hear the results of the teams' work.**

8. **Display a transparency made from *Report Form for Firm A* and use it to guide the discussion by asking teams from Firm A to present their answers to the questions (a different team should answer each question). After one team has offered an answer, invite questions and additional comments from the class.**

   To keep all students involved in both discussions, invite students from the other firm to contribute to the discussion by asking questions and even offering suggestions, as appropriate.

Question 1 What is the biological problem facing Firm A with respect to Drug X?

There is an inconsistent response to Drug X among asthma patients, that is, the drug does not work the same way on all patients.

Question 2 Describe asthma in your own words (refer to the *Team Coordinator* and *Physiologist* handouts).

Asthma is a fairly common condition that involves breathing difficulties. The bronchioles contract abnormally. It often is associated with an allergic reaction to foreign substances.

Question 3 What is Drug X designed to do for asthma sufferers (refer to the *Team Coordinator* and *Physiologist* handouts)?

The drug opens up the bronchioles so that the asthma patient can breathe more easily.

Question 4 Look at the preliminary test results (refer to the *Biostatistician* handout). Can you predict which group will be helped most or least by Drug X? For example, does the sex of the individual make a difference? Does having pets make a difference? Explain your answers.

No. There is no way to make a prediction, because there is no pattern in the response to the drug. Neither the sex of the individual nor the presence of pet dander makes a difference in the response.

Question 5 What does the example of ApoE (refer to the *Molecular Biologist* handout) suggest might be happening with Drug X? Based on this example, what might Firm A investigate?

The data indicate that response to the Alzheimer drug might be based on variations in the ApoE gene. Perhaps Firm A should explore genetic differences with respect to response to Drug X.

Question 6 Firm A's vice president for research (your teacher) will provide you with some new data. What do the new data reveal about Drug X?

There is a difference in response to the drug on the basis of the genetic variations in the patient population.

Question 7 What would be an appropriate way to prescribe Drug X?

It would be appropriate to test each asthma patient for his or her genotype to determine whether Drug X will be effective with that individual.

Question 8 Has your team solved the biological problem facing the company with respect to Drug X? What new problems has it raised?

The team's work has answered the basic biological question about response to Drug X. It has raised new questions about the ability to test all asthma sufferers. For example, how expensive is it to do that? Will physicians order the test? Will it be covered by health insurance? Who will have access to the information that results from the genetic test? How will Firm A educate physicians and other health care professionals so they understand the test and the results and so they can explain this information to their patients?

9. Repeat the same process with the teams from Firm B, but use a transparency made from Master 3.12 to guide the discussion.

Again, to keep all students involved in the discussion, invite students from the other firm to contribute to the discussion by asking questions and even offering suggestions, as appropriate.

Question 1 What is the problem facing Firm B with respect to Drug Y (refer to the *Team Coordinator* handout)?

Drug Y is a successful treatment for cystic fibrosis (CF) and is the firm's leading product. Firm B needs to keep looking ahead, however, and begin thinking about new treatments for CF that take advantage of what scientists have learned about the condition and, in the future, might be able to supplement or even replace income that the company is now receiving from Drug Y.

Question 2 Describe cystic fibrosis in your own words (refer to the *Physiologist* handout).

CF is a genetic disease that causes the body to produce an abnormally thick, sticky mucus. This mucus clogs the airways and other ducts and passages in the body and provides an ideal breeding ground for many microorganisms. CF patients have frequent airway infections and often show poor weight gain and slowed growth and development.

Question 3 What have we learned in the past few years about the cause of CF (refer to the *Molecular Biologist* handout)?

The most common CF mutation leads to one missing amino acid in the CFTR protein. The loss of this single amino acid causes the protein to be misshapen in such a way that most of it is destroyed instead of being inserted into the cell membrane. The absence of properly functioning CFTR protein in the cell membrane leads to abnormal movement of chloride ions and water in and out of the cell and production of thick, sticky mucus.

Question 4 What is Drug Y (and most other current treatments) designed to do for CF patients (refer to the *Physician* handout and discuss what goes in the last column of the table provided)?

Most existing treatments for CF focus on alleviating the symptoms of the disease, for example, removing airway mucus, reducing infection, and improving nutrition. Students should discover this by completing the last column in the table provided on the *Physician* handout.

Question 5 Firm B's vice president for research (your teacher) will provide you with some new information. What clue does this new information provide about how Firm B might approach developing new treatments for CF?

The important clue that students should gain from this new information is that understanding the biological basis of CF has allowed these researchers to propose a way to correct the problem in CF cells. This is a different approach to treatment than treating its consequences.

Question 6 What new approaches do you recommend Firm B consider as it attempts to design and develop one or more new treatments for CF?

Students will not be able to suggest detailed approaches to developing treatments, but they should be able to propose general approaches that address each of the items on the flow chart on the *Molecular Biologist* handout. For example, students might suggest developing treatments that would correct or replace the defective CF genes; replace the missing amino acid in the CFTR protein; cause the CFTR protein to fold properly despite the missing amino acid; prevent the defective CFTR protein from being destroyed before it reaches the cell membrane; introduce functional CFTR protein into the cell from another source; or create another mechanism in the cell that would regulate the movement of chloride ions.

Question 7 Has your team solved the problem facing the company with respect to Drug Y? What new problems has it raised?

No, the team has not "solved the problem" facing the company, but it has suggested several directions that the company may want to investigate as it develops new CF treatments. New problems that the team's work has raised include problems common to all development of new drugs: deciding on an approach to try, allocating funds to pay for development and clinical testing, and going through the process of gaining FDA approval for the new treatment.

10. Challenge the students to generalize what they have learned by answering the following questions:

- **How is genetic variation related to the use of drugs?**

  Students should understand that genetic differences between people may cause them to respond differently to therapeutic drugs. As scientists begin to detect such genetic differences, physicians will become more sensitive to individual variation in response to drugs and may

You may wish to ask the students who worked on Firm A's problem to answer the questions related to Firm B's problem, and vice versa.

even begin to prescribe drugs based on differences in genotype.

- **How will pharmaceutical companies likely use our increasing understanding of human genetic variation?**

  Pharmaceutical companies may begin to design drugs that are intended for people who have certain genotypes. They also may resurrect products that were not viable in the past because of their unpredictable, negative side effects on certain people.

- **How can discovering the genes associated with genetic disorders help scientists develop new approaches to treatment?**

  As Figure 6 shows, mapping and cloning the genes associated with genetic disorders helps scientists discover their underlying biochemical mechanisms, and this can suggest new approaches to treatment.

Refocusing students' attention on the opening statement draws them back to the activity's major concept.

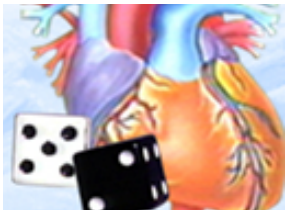
Another way to raise these issues with students is to display a transparency made from Figure 6 and ask students to explain how the activity they just completed relates to the beginning and end points of the arrows on the diagram.

11. **Display again the transparency you made from *Molecular Medicine Comes of Age*. Ask students to explain what it means and provide examples that illustrate or provide evidence for this point.**

12. **Close the activity by asking students what they think the transparency's title means.**

Potential Extensions

Extend this activity by assigning teams of students to listen to and report on selected talks from the fall 1998 *Campus on the Mall* series co-sponsored by the National Human Genome Research Institute, the National Institutes of Health, and the Smithsonian Institute. Available on the Web at http://www.nhgri.nih.gov/DIR/VIP/SI/, this series of slide-illustrated audio lectures provides the layperson with an insider's tour of recent genetic research and a glimpse into the medicine of the future.



Activity 4

Are You Susceptible?

At a Glance

Focus: Students play a game to explore the relationship between genetic variation and environmental factors in the onset of heart disease and consider the implications for disease prevention of increased knowledge about genetic variation.

Major Concepts: Studying the genetic and environmental factors involved in multifactorial diseases will lead to increased diagnosis, prevention, and treatment of disease.

Objectives: After completing this activity, students will

- understand that all disease, except perhaps trauma, has both a genetic and environmental component;
- recognize that certain behaviors can increase or reduce a person's risk of experiencing certain medical outcomes; and
- understand that the ability to detect genes associated with common diseases increases the prospects for prevention.

Prerequisite Knowledge: Students should understand the concept of a gene.

Basic Science-Health Connection: The last few years of research have seen a gradual transition from a focus on genes associated with single-gene disorders to an increasing focus on genes associated with multifactorial diseases such as cancer, heart disease, and diabetes. In this activity, students investigate the contribution that genes associated with heart disease might make to its development in an individual's life and consider the implications of this knowledge for behavior.

Introduction

Activity 3, *Molecular Medicine Comes of Age*, and Activity 4, *Are You Susceptible?*, focus students' attention on the practical, medical applications of understanding human genetic variation at a molecular level. Activity 3 looks at treatment options that become possible with the discovery and sequencing of a disease-related gene. In contrast, Activity 4 focuses on the likelihood that genetic testing for common, multifactorial diseases will increase in the future and invites students to consider the prospects for this information to help individuals make wise decisions about their personal health. Specifically, Activity 4 uses heart disease as an example of the common, multifactorial diseases that constitute the bulk of the health care burden in the United States and other developed countries. The activity builds on the treatment of variation in the prior activities and sets up the discussion of ethics that is central to Activity 5, which deals with genetics and cancer.

For the most part, the treatment of genetics in the high school curriculum focuses on single-gene traits. In addition, most of the single-gene traits discussed in the curriculum are disorders, because they provide reasonably

straightforward examples of Mendelian patterns of inheritance. Research in human genetics, however, increasingly addresses multifactorial traits, that is, traits that result from the interaction of multiple genes and environmental factors. Among the multifactorial traits that come most quickly to mind are those behavioral characteristics that are controversial and that often attract media attention, for example, intelligence, sexual preference, aggression, or basic personality traits such as novelty-seeking behavior or shyness. Research into the relative genetic and environmental contributions to behavioral traits has been uneven and is confounded by the difficulty of defining and measuring the phenotypes in question with any degree of accuracy and reliability.

A more productive area of active investigation involves the multifactorial diseases that are among the leading causes of sickness and death in developed countries, for example, heart disease, cancer, diabetes, and even psychiatric disorders such as schizophrenia and bipolar disease (manic-depressive illness). Already, research has uncovered genetic markers, and in some cases specific genes, that are associated with the development of these maladies; more genetic associations are sure to emerge as research into human genetic variation expands.

The identification of more genetic associations raises the virtual certainty of genetic testing for common, multifactorial diseases. Genetic testing is not a new phenomenon; it is done routinely to determine the risk for or presence of a number of single-gene disorders, including examples of Mendelian inheritance in the high school curriculum: Tay-Sachs disease, cystic fibrosis (CF), Huntington disease, phenylketonuria (PKU), and Duchenne muscular dystrophy. The predictive power of these tests lies in their technical reliability and the direct connection between gene and phenotype. Although there is considerable variation in symptomology for many single-gene disorders, the presence of the gene (or genes) does result in the generally recognized phenotype.

Our knowledge of the biological relationship between gene and phenotype is much less certain for multifactorial diseases. It is clear, for example, that genetic factors contribute to the risk for early onset heart disease, but the exact relationship is as yet unclear, as is the case for the relationship between certain genetic markers and the risk of schizophrenia. In these cases, the distance between gene—or genes—and phenotype is greater than it is in single-gene disorders, likely because of a host of environmental variables whose influences on phenotype are difficult to discern.

Genetic testing for common, multifactorial diseases will affect more people than does testing for relatively rare, single-gene disorders. Many of the same ethical and policy questions will apply—privacy and confidentiality, for example—but the uncertainty inherent in genetic testing for multifactorial

disease will introduce some new challenges for the public, chief among them the notions of susceptibility and risk. One may learn from a "positive" test that one is susceptible to developing the disease in question, but that will not mean that one is destined to develop the disease. Nor will a "negative" test mean that one definitely will not develop the disease. In addition, while one may learn that there is an increased *relative* risk of developing a given disease—that is, a risk that is increased above the risk for the general population—the *absolute* risk may still be quite low.

It is likely that a deeper understanding of both the molecular basis of common, multifactorial diseases and the advent of genetic testing for these diseases will improve the climate for the development of more focused clinical interventions and for preventive medicine. Multifactorial diseases tend to develop later in life than do single-gene disorders, which generally exact their toll in infancy, childhood, or adolescence. There is, therefore, more opportunity to ameliorate the effects of multifactorial disease through a combination of medication and environmental modification. That, of course, requires a partnership between patients and health care providers to identify and modify the environmental variables that magnify one's genetic risks. That is the ultimate message of this activity.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- Master 4.1, *Rolling the Dice* (make 1 copy per student)
- Master 4.2, *Thinking About the Game* (make 1 copy per student)
- dice (1 die per student)
- relevant genes envelopes (make 1 envelope per student)

  To make a classroom set of relevant genes envelopes, first make as many copies of Masters 4.3–4.6 as you need to provide one-fourth of your class with the genetic risk indicated on each master. To minimize copying, each master contains four of the same statements. Insert one statement into each envelope and label the envelope "Relevant Genes."

Procedure

1. **Begin the activity by asking students to suggest definitions of the term "risk." You might prompt the discussion by asking the students to think about risky behaviors that are a part of adolescence. Write three or four of their definitions on the board.**

   Students may suggest that "risk" refers to the chance that something bad or negative will happen, as, for example, "the risk" involved with dangerous behaviors. Help students see that one way to think about risk is in terms of one's chance of experiencing a particular event. For example, if a person performs aerial acrobatics on skis, he or she has some "risk" of getting hurt.

2. **Ask students whether they think risks can be modified. For example, ask them if there is any way they can modify their risk of being robbed or their risk of heart attack or cancer.**

   Answers will vary.

3. **Read the following story to the students:**

   Death of an Olympic Champion*

   Ekaterina Gordeeva and Sergei Grinkov, young Russian figure skaters, had won two Olympic gold medals in the pairs competition and were expected to continue dazzling audiences and judges for years into the future. In November 1995, however, 28-year-old Sergei suddenly collapsed and died during a practice session. He was a nonsmoker, he was physically fit, and there had been no warning signs. What happened to cause this young athlete's early death?

   *Source: Courtesy of Sinauer Associates, Inc., from Mange and Mange: *Basic human genetics*, Second Edition, 1999.

4. **Explain that Sergei Grinkov was born with a mutation [called *PL(A2)*] in a single gene that affects the formation of blood clots. The mutation causes clots to form in the wrong places at the wrong time. If such a clot forms in one of the arteries that supplies the heart, a heart attack can result. Ask the students to consider whether this mutant allele influenced Sergei Grinkov's risk of a premature heart attack.**

   The mutant allele increased Grinkov's risk of premature heart attack *relative* to the risk for the general population. Relative risk is the risk for any given person (or group) when considered in relation to the rest of the population. One may have an elevated relative risk, but still have a low *absolute* risk. For example, one may have an increased risk of 20 percent above the risk for the general population, but may still only have a 5 percent risk of suffering the disease in question by, say, age 50.

5. **Ask the class to suggest ways that Sergei Grinkov could have modified his behavior had he known he was at increased risk for premature heart attack.**

   Given that this single-gene disorder affects the clotting process, it likely would have been difficult to reduce the risk of heart attack by modifying the environment. There is some indication that the PL*(A2)* mutation can interact negatively with increased cholesterol levels. If, for example, plaques formed by excess cholesterol break off from the lining of a coronary artery and create a lesion in a blood vessel, the *PL(A2)* mutation can cause the formation of a clot that impedes blood flow, resulting in a heart attack. Maintaining low cholesterol levels through diet and exercise, therefore, might reduce the risk of premature heart attack for a person who carries the *PL(A2)* mutation.

6. **Explain to the students that premature heart attacks resulting from single-gene disorders are uncommon. Most heart attacks occur later in life and result from a combination of genetic and environmental factors that produce atherosclerosis, the build-up of cholesterol deposits in the arteries. In this activity, students will have an opportunity to explore the idea of medical risk and learn how genetic analysis is helping us understand and define people's risks in new ways.**

7. **Distribute one copy of Master 4.1, *Rolling the Dice,* to each student and direct the students to work in teams of three to play the game described.**

   Give the students about 10 minutes to finish the game.

8. **Ask how many students suffered a fatal heart attack. Determine at which life stages the heart attacks occurred and record this information on the board.**

9. **Ask the students how the game is and is not like real life.**

   The game is like real life in that life expectancy depends on many risk factors. The game is not like real life because students rolled the die to determine what their risk factors would be instead of making personal choices. The game also involved only environmental risk factors, not genetic factors. If students fail to mention that the game does not address genetic risk factors, try to elicit that response by asking about Sergei Grinkov.

10. **Acknowledge the importance of considering genetic risk factors in the development of heart disease and ask students what effect(s) factoring this information into the game might have.**

    Answers will vary. Because of the example of Sergei Grinkov and because of their own sense that sometimes heart disease tends to "run in families," students may think that including genetic factors in the game will inevitably have a negative effect. You may choose to point out that for some people, the effect might be positive, or let students discover this in Step 11.

11. **Distribute one relevant genes envelope to each student and explain that this envelope contains information about his or her genetic risk for a fatal heart attack. Ask the students to open the envelopes and share their heart points until you have addressed all four values: -10, 0, +10, +40. Point out that the genetic risk falls off rapidly as genetic relatedness decreases, from 40 points for first-degree relatives to no points for third-degree relatives. Explain that this is the case generally for multifactorial diseases.**

12. **Distribute one copy of Master 4.2, *Thinking About the Game,* to each student and ask students to complete the worksheet to compare the results of the game with and without considering genetic factors.**

This part of the game is futuristic, in that at this time, we either do not have the technology available to determine each person's individual risk, or, if this technology is available, conducting such genetic testing is not yet a regular part of medical care. Nevertheless, you may wish to point out to students that with the rapid pace of our progress in understanding the molecular basis for disease, such testing may well be in their future.

You may wish to collect your students' answers to these questions to evaluate how well they understand the issues involved.

13. Conclude the activity by inviting each team to offer its answer to one of the questions on Thinking *About the Game*. Then, invite other teams to contribute additional insights or information or to challenge ideas expressed by the team answering.

Question 3 Remember, if you exceeded 85 points in any life stage, you have had a fatal heart attack. What effect did including your points for genetic risk have on your outcome?

Answers will vary. Including the genetic data may have pushed some students over the threshold to a heart attack. Others may have escaped a heart attack because of the protective effects of their genes, while still others may have experienced no change. The important point is that the environmental risks—the choices they made—have been played out against a genetic background, which differs for each person.

Question 4 Think about the choices you made in each life stage.

a. Did everyone make the same choices?

No, each person made somewhat different choices.

b. Were all of the choices equally risky?

No, some of the choices carried greater risks than others, and some decreased the risks.

c. Were the risk factors associated with the choices reversible?

Most of the risk factors were reversible—smoking, exercise, and stress, for example.

d. Were the choices under personal control?

In the game, choices were made on the basis of a roll of a die. In life, however, most of these choices are under personal control.

Question 5 Now, think about the effects of genetic risk factors in each life stage.

a. Does everyone have the same genes?

No, each person (except identical twins) has different genes.

b. Did all of the genetic factors have the same effect?

No, some genetic factors had negative effects, some were neutral, and some provided protection.

c. Were the genetic factors reversible or under personal control?

We cannot change the genes with which we are born. We can, however, sometimes modify the *effects* of those genes by modifying the environment, for example, by changing some of our behaviors.

Question 6 Assume that genetic testing showed that you were at increased risk for a fatal heart attack 20 years from now. Would you want to know? Why or why not? Would that information cause you to change your behavior? If not, what kind of information or event would cause you to change your behavior?

Answers will vary, but the assumption is that knowledge of increased genetic risk would cause one to modify his or her behavior to reduce the environmental risk factors. A very important point here is that a family history of heart disease is an indication of increased genetic risk, even if we are not yet able to identify predisposing genes and attach some risk figure to them. The literature on health and behavior—and personal experience—demonstrates that people do not always change their behaviors in the face of well-documented risk. Cigarette smoking is perhaps the classic example that applies well to adolescents. Some people will not change their behavior even in the face of serious illness.

Question 7 We know about only a few genes that affect the likelihood of a heart attack, and we have the ability to test for even fewer of them. In the future, we certainly will learn about more of these genes. How will an increased knowledge of the genetic factors associated with heart disease have a positive impact on individuals and society? How will it have a negative impact?

Increased knowledge about such genes will lead to increased testing and the development of new clinical interventions. Our ability to test for genes that predispose to heart disease will mean that we can detect those genetic susceptibilities sooner and act on them more quickly, for example, with drugs targeted at the specific biochemical defects involved and with modification of risky behaviors.

The frequency of heart disease, and other common, multifactorial diseases, means that genetic testing will be applied to many more individuals, with attendant concerns about how we use the results of genetic testing. In addition, genetic testing for multifactorial diseases will require education of the public and health care providers about the meaning of susceptibility and predisposition. Activity 5 explores some of these issues in more detail.

Question 8 Our ability to detect genetic variations that are related to common diseases will improve. How might that ability shift some of the responsibility for health care from physicians to individuals?

This question is designed to draw students' attention back to the activity's major concept.

If we know that we are at increased genetic risk for a particular disease, we can try to avoid those environmental factors, such as risky behaviors, that increase the risk further. Many health care professionals think that increased understanding of genetic variation will provide an important impetus to preventive medicine. Prevention will

require a close partnership between health care providers and consumers. Health care specialists may be able to provide us with tests to uncover our genetic predispositions, but it will be up to each one of us to avoid increasing those risks by engaging in high-risk behaviors. In short, each of us will have to assume more responsibility for our own health. This requires active participation by the individual and is very different from the prevailing model, which is based not on prevention but on treatment after the disease occurs. In the current model, the individual (the patient) generally is a rather passive recipient of health care.

Activity 5

Making Decisions in the Face of Uncertainty

At a Glance

Focus: Students analyze a CD-ROM-based case study about a family's decisions related to testing for particular genetic variations that increase susceptibility to breast cancer and consider how understanding the related science can help people make decisions in uncertain circumstances.

Major Concepts: Our growing understanding of human genetic variation will allow us to identify genes that are associated with common diseases such as cancer. Genetic testing to identify individuals who have variations that make them susceptible to certain diseases can help people make decisions in uncertain circumstances and holds the prospect for more effective prevention and treatment. However, this capability also raises difficult questions that illustrate the personal and social implications of biological research.

Objectives: After completing this activity, students will

- recognize that our understanding of science can help us analyze and make decisions in uncertain circumstances;
- understand that the ability to identify susceptible individuals through genetic screening and testing holds the prospect for more effective prevention and treatment;
- understand that our ability to identify individuals susceptible to particular diseases also raises difficult questions about the uses of genetic information;
- be able to explain that although it is possible to analyze these questions rationally and civilly, people still may disagree on the answers; and
- understand that science can tell us what we can and cannot do, but we depend on an analysis of ethics and public policy (informed by a sound understanding of the science) to help determine what we should do.

Prerequisite Knowledge: Students should understand that cancer is characterized by uncontrolled growth of cells. Students also should understand that all cancer is fundamentally genetic because it results from the loss of genetic control of the cell cycle. That does not mean that all cancer is hereditary. The form of breast cancer that this activity addresses is one of the hereditary cancers, but it is responsible for only about 5 percent of all breast cancers. Most breast cancers arise from somatic mutations and thus are not hereditary.

Basic Science-Health Connection: This activity highlights the remarkable progress scientists are making in identifying genes related to multifactorial diseases such as cancer and focuses students' attention on the implications such discoveries have for personal health and decision making.

Introduction

This activity offers students the opportunity to apply their understanding of human genetic variation to a fictional case study involving a potentially painful set of decisions that various members of a family have to make. Teams of students analyze the case of a woman, Beth, who is concerned that she may carry a variant of either the *BRCA1* or *BRCA2* gene that predisposes to breast cancer. The case study is presented in five segments during which Beth makes two key decisions: (1) to proceed with being tested for altered forms of these genes and (2) after she develops cancer in one breast, not to have a prophylactic mastectomy of the other breast. Students analyze each segment by discussing a set of questions related to the underlying science and to the ethical and policy dilemmas raised by the decisions.

The activity's fundamental purpose is to help students see that an understanding of science and a clear, systematic analysis of options can help us make decisions in uncertain circumstances. Beth has a family history of breast cancer, a form of cancer that kills more than 40,000 women in the United States each year. Information about the presence of the altered gene could help her and her physician be more alert to the possibilities of her developing cancer.

On the other hand, she already is practicing the guidelines recommended to increase the chance of early detection should cancer develop. Furthermore, as students learn, breast cancer related to the presence of an inherited altered gene accounts for only 5 percent of the new cases of breast cancer diagnosed each year, and even if Beth is shown *not* to carry the altered gene, a certain risk of breast cancer remains. Thus, the decision whether to be tested is complex and is made more so by uncertainty related to the normal human genetic variation that exists among humans. Our understanding of genetic factors that can predispose individuals to certain cancers, while increasing, still is far from complete. The question about whether Beth should request prophylactic mastectomy of both breasts after she develops cancer in one breast is equally complex.

Materials and Preparation

You will need to prepare the following materials before conducting this activity:

- Master 5.1, *Analyzing the Issues* (make 1 copy per student)
- *Human Genetic Variation* CD-ROM (1 per team)

Follow the instructions on page 23 to load the CD-ROMs on the computers the students will use.

Note to teachers: If you do not have enough computers equipped with CD-ROM drives to conduct this activity, you can use the print-based alternative. To view and print the instructions and masters for this alternate activity, load the CD onto a computer and click the Print button on the main menu screen. The computer will display a screen showing the resources available for printing from the CD; click on the button labeled Non-CD Lesson Plan from the choices available for Activity 5, *Making Decisions in the Face of Uncertainty*. This will reveal the lesson plan and the masters for the alternate, non-CD-based lesson. Click Print again to print these resources.

Procedure

Tip from the field test. Teachers who tested this activity raised two cautions.

- Students became so engaged in Beth's story that they lost sight of the major messages about genetic variation and its relationship to complex disease. Remind your students that Beth's difficult decisions arise because of progress in basic science that allows us to detect such genetic variations.
- Students tended to confuse the test for mutations in the *BRCA1* and *BRCA2* genes with a test for cancer itself. Be sure to clarify this distinction. The genetic test identifies forms of the *BRCA1* and *BRCA2* genes that can increase one's likelihood of developing cancer. It is not a test for cancer.

1. **Open the activity by asking students whether they know anyone who has had breast cancer. Invite those students who wish to briefly describe their relationship to the individual involved to do so.**

   With approximately 1 in 8 American women developing breast cancer in their lifetimes, it would not be unusual for one or more of your students to be involved personally with this type of cancer. It may be that the student's mother or another family member has had or currently has cancer. For some of those students, discussions of cancer may be disturbing. We suggest that you watch your students for signs of discomfort (for example, tearfulness, reluctance to begin the activity, unusual silence or reticence) and provide appropriate support.

2. **Direct students to organize into their teams and watch the CD-ROM-based videos *Making Decisions in the Face of Uncertainty* (the total running time is about 10 minutes). This first time through, ask students simply to watch and listen so they can get a sense of the complete case.**

3. **Distribute one copy of Master 5.1, *Analyzing the Issues*, to each student and explain that now the class will view the videos again, one segment at a time. Suggest that students take notes and list questions that occur to them as they watch each segment, then respond to the related questions on *Analyzing the Issues*. Discuss each segment in turn, as students complete it, using the questions on *Analyzing the Issues* as a guide. Address any other questions the students raise as well.**

   If students raise questions about the science or legal/policy issues that you and they cannot answer with the materials provided, suggest that someone pursue those answers outside of class.

Segment 1: Considering the Test

Question 1 What decision does Beth have to make?

Beth has to decide whether to have the test for mutations in her *BRCA1* and *BRCA2* genes. Your students might be interested in the financial aspects of the test. As of mid-1999, when this program was written, the laboratory cost for the combined test for *BRCA1* and *BRCA2* was about

$2,500. The costs for the associated genetic counseling were about $250 to $300. Insurance coverage varies depending on the carrier.

Question 2 Who might be affected by Beth's decision?

Beth, her husband, her mother, her sisters, her teenage daughter, and her daughter's future husband (if she marries).

The identification of mutations that predispose individuals carrying them to cancer is an excellent example of how basic research in science yields results that benefit society. As students complete the activity, challenge them to think about the benefits that Beth and her family gain as a result of this knowledge. Ask students to summarize their ideas as you close the activity in Step 4.

Question 3 What arguments support having the test?

This is a good opportunity to make certain that the students understand the underlying science in this case study. Files in the *Reference Database* on the CD-ROM will help students learn about the science. Students can access those files on their own, if you have enough CD-ROM players, or you can print the materials and distribute them.

Beth no longer will be uncertain about her status with respect to *BRCA1* and *BRCA2*. She will be able to make some other decisions, and she will be able to inform other family members about whether they are at risk for carrying a mutated form of one of the genes. Note that Beth says, with respect to a potentially negative genetic test, "You find out that you're safe." Ask students to comment on this remark. Emphasize that this test identifies only one type of risk factor for breast cancer. Simply because one does not have the particular mutations identified in this test does not mean that one "is safe" from developing breast cancer. There likely are other unknown genetic variations that can increase one's risk. Furthermore, only a small proportion of breast cancer is hereditary. Beth's comment about birth control pills provides an opportunity to discuss the constantly changing nature of scientific knowledge and to point out the environmental contributions to cancer.

Question 4 What arguments support *not* having the test?

Beth may not want to know. She also will not have to worry about whether she should share potentially positive test results with other members of the family. She will not have to make tough decisions about detection and/or prevention options (for example, prophylactic mastectomy), none of which is 100 percent effective.

Question 5 What factors do you think Beth and Charlie should consider in making their decisions?

Answers will vary, but be alert for misconceptions about the underlying science.

Segment 2: A Family Question

Question 1 What new facts have you learned about breast cancer?

In testing for genes related to cancer, it is helpful to test a family member who already has had the disease. Not all cancers are heredity. The form of cancer that Beth's mother has may not be heredity. If it is hereditary, it may be associated with a gene not yet identified by scientists.

Question 2 What are some of the family issues that arise in this counseling session?

Beth's mother feels guilty about her breast cancer and about the possibility that she has passed on the associated mutation. The issue of blame also arises, as well as the question of what Beth will do with the information if the test is positive. Note that the counselor stresses the importance of privacy and confidentiality. Emphasize for your students that genetic counselors are trained to handle the social and emotional aspects of counseling as well as the scientific aspects.

Question 3 What reasons does the genetic counselor give for not testing Jennifer? Do you agree that children under 18 should not be tested?

The counselor's reasons are rather nonspecific, simply that "teenagers often have different perspectives about developing breast cancer." Students' views on the testing of children under 18 will vary. Insist, however, that they provide concrete explanations for their positions and be alert to misunderstandings of the science.

The decision for a health care provider to conduct a genetic test is based on a variety of factors. Health care professionals are trained to reduce risks to their patients, including psychosocial risks. Anxiety and depression may arise in response to a positive test. A similar issue received attention in the mid-1980s, when health care professionals had to decide how to handle testing for exposure to the AIDS virus, HIV. At that point, the connection between a positive test for exposure to HIV and development of the fatal disease AIDS was not yet clear (although the correlation has since been established to the satisfaction of virtually all scientists). Keep in mind that not everyone who inherits an altered form of *BRCA1* or *BRCA2* develops breast cancer; thus, knowing that one carries such an allele may trigger needless anxiety.

Other factors that a health care provider considers when discussing genetic testing include the following questions:

- Can the related disorder, once diagnosed, be treated? In some cases, for example, Huntington disease, there are no treatments currently available that can help a person who tests positive.
- Does the patient exhibit symptoms, or is the order for a test based on family history alone?
- Do the benefits outweigh the harm brought about by knowledge of the test results?

The issue becomes even more complex when the patient to be tested is a minor, that is, under 18 years of age. The request for a genetic test may come from the parents or from the minor. When the minor is an

adolescent, the issue becomes particularly complicated because the patient may exhibit a considerable degree of autonomy regarding his or her health care decisions. Experts agree that in these cases the primary goal of genetic testing should be to promote the child's well-being. For example, the child who tests positive may be overindulged or may be treated as a scapegoat. Both of these problems can occur, however, even in the absence of testing. The testing of a child (or indeed any other family member) also has implications for all members of the family. In some cases, this forewarning will be welcomed; in others, it may be unwanted. Genetic testing of a child will ease some aspects of uncertainty, but people differ greatly in their response to such news.

In the case of genetic testing for mutations in the *BRCA1* gene, most health care providers and genetic testing centers adhere to a policy that denies tests to minors. This denial extends to requests from the parents, who are the legal guardians of the child's health. The psychological effects can be mixed. Whereas some individuals prefer the release from uncertainty, others could view a positive result as a death sentence and react in ways that are destructive to themselves or their families. Genetic testing requires informed consent, and some geneticists argue that this requirement automatically rules out children, and even teenagers, who generally are judged incapable of providing such consent. This view of minors, however, may be far too broad and may not be realistic. Some specialists are beginning to recognize that some adolescents and young children have sufficient autonomy in consent and decision making to make such decisions, and recommend that the desires of these youths should be taken into account. In any event, one must weigh the *balance* of potential harm and benefit in reaching a decision about testing a minor.

One outcome of the current policy is to delay the decision to test until the individual is an adult and can make the decision, rather than letting parents remove this option by making the choice themselves. Note that a *change* in policy most likely would result in *parents* being permitted to make the decision, rather than leaving the decision to the minor in question. Either way, issues of ethical decision making will arise.

Question 4 Beth's mother says, "I'm not sure more information is better." Do you agree with her? Explain your answer.

Answers will vary.

Segment 3: The Test Results

Question 1 Beth and her mother have had the genetic test. What new information have we learned?

Beth and her mother are positive for the *BRCA1* mutation. Beth has a lifetime risk of perhaps about 60 percent of developing breast cancer. This number is down from original estimates, which were as high as 87 percent. Some recent data suggest an even lower risk figure than 60

percent. In fact, as is often true when a new medical test becomes available, the exact figure is still not yet known. Further, it appears that the exact risk figure may vary, depending upon the exact mutation in the *BRCA1* that an individual woman carries.

Students also have learned that Beth may *not* develop breast cancer even though her test was positive and that Beth can do a number of things (breast self-examinations and mammograms, for example) to help detect any cancer early and, therefore, to begin early treatment.

Remember to emphasize that Beth and her mother were tested for mutations in the *BRCA1* and *BRCA2* genes, not for cancer.

Segment 4: A Diagnosis of Breast Cancer

Question 1 What new information have we learned about Beth?

It is now three years after the genetic test, and Beth has been diagnosed with cancer in one breast. There is a high risk of cancer in the other breast.

Question 2 What major decisions do Beth and her husband discuss in this segment?

First, they discuss whether Beth should have both breasts removed, and second, they consider whether to tell Jennifer that she is at risk for the *BRCA1* mutation. Note that even removal of both breasts does not guarantee that the cancer will not appear elsewhere or even appear in the remaining breast tissue.

Question 3 What do you think Beth and Charlie should do? Why?

Answers will vary, but make certain that students provide sound explanations for their positions. Again, make sure that the science is correct.

Segment 5: Jennifer's Decision

Question 1 What new information emerges in this segment?

Beth has had a lumpectomy, and Jennifer has not been tested. Emphasize that the chance of survival increases with early diagnosis.

Question 2 What is Jennifer's primary concern about the test?

She is concerned that potential employers and insurers will discriminate against her if they find out she has a high relative risk for breast cancer.

Question 3 Do you think employers or insurers should be able to deny employment or insurance to a person who has a genetic predisposition to a disease such as cancer? Explain your position.

Answers will vary. Inform students that at present many states have laws that prohibit health insurers from accessing and using genetic information in a discriminatory way. In addition, the federal Health

Insurance Portability and Accountability Act (HIPAA) prohibits those who issue commercial, employer-based, group health plans from discriminating against individuals on the basis of information gained from genetic tests.

Regarding employment discrimination, the Equal Employment Opportunity Commission extends "Americans with Disabilities" protection to individuals who experience discrimination based on genetic information related to illness, disease, or other disorders.

4. **Close the activity by challenging students to identify the questions that now face Jennifer, Beth's daughter, about her own health and personal welfare. Encourage students to think deeply about these questions. For each question that they identify as facing Jennifer, have them determine her options and begin to identify arguments that she might use in support of choosing one option over the other. Invite neighboring teams to discuss these questions. Then, use the following questions to stimulate a brief, final class discussion about the activity.**

Use students' answers to these questions to assess their understanding of the activity's major concepts.

- **Our understanding of and ability to identify genetic differences among us has increased remarkably in the last few decades and continues to increase. How might Beth's and Jennifer's decisions have been different 50 years ago? What advantages does our knowledge of human genetic variation bring us? What questions does it also raise?**

  Fifty years ago, Beth and Jennifer would not have been faced with the decision about whether to have these genetic tests. They would have had the option of lumpectomy or radical mastectomy if cancer were discovered. Our increased knowledge of human genetic variation has improved our understanding of the relationship between certain variations and disease and enabled us to test for some of these genetic variations. New knowledge and abilities, however, raise questions about whether we should test and about what we should do with the resulting information. The ability to test also raises the question of whether we should or will come to treat people who are genetically predisposed to illness as if they already are sick, even if they are not and may never be. These people are sometimes referred to as the "asymptomatically ill."Ask the students to react to that designation.

Insist that students apply the saying to this activity. Then, to close the module effectively, ask students to apply the saying to our growing knowledge of human genetic variation (in general). Students should see that this knowledge offers us new opportunities and choices, but it also brings new challenges.

- **How does this activity illustrate the old saying that knowledge plus choice equals power?**

  The more we learn about a given situation—for example, our status with respect to the *BRCA1* and *BRCA2* genes—the greater our ability is to make decisions and control our own destiny, so long as the choices are available. The importance of choices emerges in this activity in at least two ways. First, Beth and Jennifer must be confident that information that results from the test will not be used against them. Otherwise they may feel, as Jennifer does, that they are not

really free to chose whether to have the test. Second, the general policy not to test children under 18 for mutations in the *BRCA1* or *BRCA2* genes has restricted the choices for people under 18. This limits their access to knowledge about themselves and restricts their power to make decisions about their own lives.

Potential Extensions

Extend this activity by challenging students to connect what they learned in Activity 5 with what they learned in the two preceding activities. For example, ask students to connect Activity 5 with Activity 3 by suggesting how discovering mutations that predispose people to the development of cancer might help scientists develop new approaches to treating cancer. Then, assign students to learn more about this question by reading the article "Making headway against cancer" by J. Rennie & R. Rusting in the September 1996 special edition of *Scientific American*.

Likewise, connect Activity 5 with Activity 4 by asking students to research how discovering mutations that predispose people to the development of colon cancer has led to the creation of screening and counseling programs that are already saving lives by alerting people to their increased risk and helping them make good lifestyle and health care choices.

Additional Resources for Teachers

The following resources may provide additional background information about human genetic variation for you and your students.

Resources on the World Wide Web

National Human Genome Research Institute
http://www.nhgri.nih.gov

This site provides current and authoritative information about the work of the National Human Genome Research Institute and about the scope and progress of the Human Genome Project. It includes links to all of the genome centers in the United States and around the world, as well as to the major mapping, sequence, and structure databases. It also includes information about the Ethical, Legal, and Social Implications of Human Genetics Research (ELSI) program.

The address http://www.nhgri.nih.gov/DIR/VIP/ takes you directly to the home page of the Office of Science Education and Outreach, which provides access to a variety of educational resources, including a talking glossary of genetics, printable illustrations and explanations of important terms and current techniques in molecular genetics, and schedules and (in some cases) the full texts of workshops and presentations on a wide range of topics related to human genetic research.

The address http://www.nhgri.nih.gov/DIR/VIP/SI takes you directly to the Campus on the Mall Lecture Series on Genetics, a series of eight slide-illustrated lectures presented as a joint effort between researchers in NHGRI's Division of Intramural Research and the Smithsonian Institute. Geared toward the layperson and suitable for high school students, the course provides a tour of current research in human genetics and a glimpse into the genetic medicine of the future. Topics include the Human Genome Project, techniques involved in cloning and mapping genes, genes related to human behavior, the genetics of cancer, gene therapy, and issues related to genetic testing.

Department of Energy
http://www.ornl.gov.hgmis/publicat/primer/intro.html

This site, funded and developed by the Human Genome Project of the U.S. Department of Energy, provides a wealth of information on the Human Genome Project and modern genetic research, including a *Primer on Molecular Genetics* and other resources for teachers.

DNA Learning Center
Cold Spring Harbor Laboratory
http://vector.cshl.org

This site offers a variety of unique educational tools, such as bioservers that allow users to dabble in the emerging field of bioinformatics; articles and animations about specific topics in genetics, and interactive exercises that allow students to solve real-life genetics problems using authentic research tools. This site also includes *DNA from the Beginning*, an online, animated primer of genetics targeted at high school students and other people who do not have extensive science backgrounds.

Blazing a Genetic Trail
Howard Hughes Medical Institute
http://hhmi.org/GeneticTrail

Developed by the Howard Hughes Medical Institute (HHMI), this is an interesting, highly readable set of stories about the work of HHMI investigators in molecular genetics. The HHMI

home page (http://hhmi.org) also provides a-delightful feature called *Becoming a Scientist* in-which each month, a new video introduces an-HHMI investigator who talks about what it takes-to become successful as a practicing scientist. -

Access Excellence-
http://www.accessexcellence.org-

The section *About Biotech* on this site contains arti-cles about new developments and ethical issues in-biotechnology, a biotechnology career guide, infor-mation on techniques used in biotechnology, and a-wide variety of printable images useful in teaching-biology.-

The Gene Letter-
The Shriver Center, Incorporated-
http://www.geneletter.org-

This site provides a series of articles about a vari-ety of topics in science, ethics, and law. Topics-focus particularly on issues in medical genetics-and change regularly, though back issues also are-available.-

National Library of Medicine-
http://www.ncbi.nlm.gov/disease-

This site provides brief descriptions, easily read by-students, of more than 60 genetic disorders.-

The DNA Files-
SoundVision Productions-
http://www.dnafiles.org/home.html-

This site provides the audio of nine one-hour pro--grams about genetic research and its applications-that aired on National Public Radio. Tapes and-transcripts of these broadcasts also are available-for ordering.-

Other Resources

Several organizations, directed at supporting indi-viduals with genetic disorders or professional-organizations, provide resources for teaching and-for the lay public.-

Alliance of Genetic Support Groups-
4301 Connecticut Avenue NW-
Suite 404-
Washington, DC 20008-
(800) 336-4363-
http://www.geneticalliance.org-

National Organization for -
Rare Disorders, Incorporated-
P.O. Box 8923-
New Fairfield, CT 06812-8923-
(800) 999-6673-
http://www.rarediseases.org-

National Society of Genetic Counselors,-
Incorporated-
233 Canterbury Drive-
Wallingford, PA 19086-6617-
(800) 872-7608-
http://www.nsgc.org-

Glossary

The following glossary was modified from the glossary on the National Human Genome Research Institute's Web site, available at http://www.nhgri.nih.gov.

allele: One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics such as hair color or blood type. In an individual, one form of the allele (the dominant one) may be expressed more than another form (the recessive one).

amino acid: One of 20 different kinds of small molecules that link together in long chains to form proteins. Amino acids are referred to as the "building blocks" of proteins.

autosomal dominant: Gene on one of the autosomes that, if present, will almost always produce a specific trait or disease. The chance of passing the gene (and therefore the disease) to children is 50-50 in each pregnancy.

autosome: Chromosome other than a sex chromosome. Humans have 22 pairs of autosomes.

base pair: Two bases that form a "rung of the DNA ladder." The bases are the "letters" that spell out the genetic code. In DNA, the code letters are A, T, G, and C, which stand for the chemicals adenine, thymine, guanine, and cytosine, respectively. In base pairing, adenine always pairs with thymine, and guanine always pairs with cytosine.

birth defect: Defect present at birth, whether caused by mutant genes or by prenatal events that are not genetic.

***BRCA1/BRCA2*:** First breast cancer genes to be identified. Mutated forms of these genes are believed to be responsible for about one-half the cases of inherited breast cancer, especially those that occur in younger women, and also to increase a woman's risk for ovarian cancer. Both are tumor suppressor genes.

cancer: Diseases in which abnormal cells divide and grow unchecked. Cancer can spread from its original site to other parts of the body and can be fatal if not treated adequately.

candidate gene: Gene, located in a chromosome region suspected of being involved in a disease, whose protein product suggests that it could be the disease gene in question.

CCR5: Mutation that confers immunity to infection by HIV. The mutation alters the structure of a receptor on the surface of macrophages such that HIV cannot enter the cell.

cDNA library: Collection of DNA sequences generated from mRNA sequences. This type of library contains only protein-coding DNA (genes) and does not include any noncoding DNA.

cell: Basic unit of any living organism. It is a small, watery, compartment filled with chemicals and a complete copy of the organism's genome.

chromosome: One of the thread like "packages" of genes and other DNA in the nucleus of a cell. Different kinds of organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes, 46 in all: 44 autosomes and two sex chromosomes. Each parent contributes one chromosome to each pair, so children get one-half of their chromosomes from their mothers and one-half from their fathers.

cloning: Process of making copies of a specific piece of DNA, usually a gene. When geneticists speak of cloning, they do not mean the process of making genetically identical copies of an entire organism.

codon: Three bases in a DNA or RNA sequence that specify a single amino acid.

cystic fibrosis (CF): Hereditary disease whose symptoms usually appear shortly after birth. They include faulty digestion, breathing difficulties and respiratory infections due to mucus accumulation, and excessive loss of salt in sweat. In the past, cystic fibrosis was almost always fatal in childhood, but treatment is now so improved that patients commonly live to their 20s and beyond.

cytogenetic map: Visual appearance of a chromosome when stained and examined under a microscope. Particularly important are visually distinct regions, called light and dark bands, that give each of the chromosomes a unique appearance. This feature allows a person's chromosomes to be studied in a clinical test known as a karyotype, which allows scientists to look for chromosomal alterations.

deletion: Particular kind of mutation: loss of a piece of DNA from a chromosome. Deletion of a gene or part of a gene can lead to a disease or abnormality.

deoxyribonucleic acid (DNA): Chemical inside the nucleus of a cell that carries the genetic instructions for making living organisms.

diploid: Number of chromosomes in most cells except the gametes. In humans, the diploid number is 46.

DNA microchip technology: Technology that identifies mutations in genes. It uses small glass plates that contain synthetic single-stranded DNA sequences identical to those of a normal gene.

DNA replication: Process by which the DNA double helix unwinds and makes an exact copy of itself.

DNA sequencing: Determining the exact order of the base pairs in a segment of DNA.

dominant: Gene that almost always results in a specific physical characteristic (for example, a disease) even though the patient's genome possesses only one copy. With a dominant gene, the chance of passing on the gene (and therefore the disease) to children is 50-50 in each pregnancy.

double helix: Structural arrangement of DNA, which looks something like an immensely long ladder twisted into a helix, or coil. The sides of the "ladder" are formed by a backbone of sugar and phosphate molecules, and the "rungs" consist of nucleotide bases joined weakly in the middle by hydrogen bonds.

duplication: Particular kind of mutation: production of one or more copies of any piece of DNA, including a gene or even an entire chromosome.

electrophoresis: Process in which molecules (such as proteins, DNA, or RNA fragments) can be separated according to size and electrical charge by applying an electric current to them. The current forces the molecules through pores in a thin layer of gel, a firm, jellylike substance. The gel can be made so that its pores are just the right dimensions for separating molecules within a specific range of sizes and shapes. Smaller fragments usually travel further than large ones. The process is sometimes called gel electrophoresis.

enzyme: Protein that encourages a specific biochemical reaction, usually speeding it up. Organisms could not function if they had no enzymes.

exon: Region of a gene that contains the code for producing the gene's protein. Each exon codes for a specific portion of the complete protein. In some species (including humans), a gene's exons are separated by long regions of DNA (called "introns" or sometimes "junk DNA") that have no apparent function.

fluoresence in situ hybridization (FISH): Process that vividly paints chromosomes or portions of chromosomes with fluorescent molecules. This technique is useful for identifying chromosomal abnormalities and gene mapping.

gene: Functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

gene amplification: Increase in the number of copies of any particular piece of DNA. A tumor cell

amplifies, or copies, DNA segments naturally as a result of cell signals and sometimes environmental events.

gene expression: Highly specific process in which a gene is switched on at a certain time and begins production of its protein.

gene mapping: Determining the relative positions of genes on a chromosome and the distance between them.

gene pool: Sum total of genes, with all their variations, possessed by a particular species at a particular time.

gene therapy: Evolving technique used to treat inherited diseases. The medical procedure involves either replacing, manipulating, or supplementing nonfunctional genes with healthy genes.

gene transfer: Insertion of unrelated DNA into the cells of an organism. There are many different reasons for gene transfer, for example, attempting to treat disease by supplying patients with therapeutic genes. There are also many possible ways to transfer genes. Most involve the use of a vector, such as a specially modified virus that can take the gene along when it enters the cell.

genetic code: Instructions in a gene that tell the cell how to make a specific protein. A, T, G, and C are the "letters" of the DNA code; they stand for the chemicals adenine, thymine, guanine, and cytosine, respectively, that make up the nucleotide bases of DNA. Each gene's code combines the four chemicals in various ways to spell out three-letter "words" that specify which amino acid is needed at every step in making a protein.

genetic counseling: Short-term educational counseling process for individuals and families who have a genetic disease or who are at risk for such a disease. Genetic counseling provides patients with information about their condition and helps them make informed decisions.

genetic map: Chromosome map of a species that shows the position of its known genes and/or markers relative to each other, rather than as specific physical points on each chromosome.

genetic marker: Segment of DNA with an identifiable physical location on a chromosome and whose inheritance can be followed. A marker can be a gene, or it can be some section of DNA with no known function. Because DNA segments that lie near each other on a chromosome tend to be inherited together, markers are often used as indirect ways of tracking the inheritance pattern of a gene that has not yet been identified, but whose approximate or exact location is known.

genetic screening: Testing a population group to identify a subset of individuals at high risk for having or transmitting a specific genetic disorder.

genetics: Study of inherited variation.

genome: All the DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA in mitochondria.

genotype: Genetic identity of an individual that does not show as outward characteristics.

germ line: Sequence of cells, each descended from earlier cells in the lineage, that will develop into new sperm and egg cells for the subsequent generation.

haploid: Number of chromosomes in a sperm or egg cell; one-half the diploid number.

heterozygous: Possessing two different forms of a particular gene, one inherited from each parent.

highly conserved sequence: DNA sequence that is very similar in several different kinds of organisms. Scientists regard these cross species' similarities as evidence that a specific gene performs some basic function essential to many forms of life and that evolution has therefore conserved its structure by permitting few mutations to accumulate in it.

homozygous: Possessing two identical forms of a particular gene, one inherited from each parent.

Human Genome Project (HGP): International research project to map each human gene and to completely sequence human DNA.

hybridization: Base pairing of two single strands of DNA or RNA.

in situ hybridization: Base pairing of a sequence of DNA to metaphase chromosomes on a microscope slide.

inherited: Transmitted through genes from parents to offspring.

insertion: Type of chromosomal abnormality in which a DNA sequence is inserted into a gene, disrupting the normal structure and function of that gene.

library: Collection of cloned DNA, usually from a specific organism.

linkage: Association of genes and/or markers that lie near each other on a chromosome. Linked genes and markers tend to be inherited together.

locus: Place on a chromosome where a specific gene is located; a kind of address for the gene.

mapping: Process of deducing schematic representations of DNA. Three types of DNA maps can be constructed: physical maps, genetic maps, and cytogenetic maps; the key distinguishing feature among these three types is the landmarks on which they are based.

marker: Also known as a genetic marker, a segment of DNA with an identifiable physical location on a chromosome whose inheritance can be followed. A marker can be a gene, or it can be some section of DNA with no known function. Because DNA segments that lie near each other on a chromosome tend to be inherited together, markers are often used as indirect ways of tracking the inheritance pattern of genes that have not yet been identified, but whose approximate locations are known.

Mendelian inheritance: Manner in which genes and traits are passed from parents to children. Examples of Mendelian inheritance include autosomal dominant, autosomal recessive, and sex-linked genes.

messenger RNA (mRNA): Template for protein synthesis. Each set of three bases, called a codon, specifies a certain amino acid in the sequence of amino acids that compose the protein. The sequence of a strand of mRNA is based on the sequence of a complementary strand of DNA.

metaphase: Phase of mitosis, or cell division, when the chromosomes align along the center of the cell. Because metaphase chromosomes are highly condensed, scientists use these chromosomes for gene mapping and identifying chromosomal aberrations.

microarray technology: New way of studying how large numbers of genes interact with each other and how a cell's regulatory networks control vast batteries of genes simultaneously. The method uses a robot to precisely apply tiny droplets containing functional DNA to glass slides. Researchers then attach fluorescent labels to DNA from the cell they are studying. The labeled probes are allowed to bind to complementary DNA strands on the slides. The slides are put into a scanning microscope that can measure the brightness of each fluorescent dot; brightness reveals how much of a specific DNA fragment is present, an indicator of how active it is.

mitochondrial DNA (mtDNA): Genetic material of the mitochondria, the organelles that generate energy for the cell.

multifactorial trait: Trait that is controlled by many genes and is also influenced by the environment.

mutation: Permanent structural alteration in DNA. In most cases, such DNA changes either have no effect or cause harm, but occasionally a mutation can improve an organism's chance of surviving and passing the beneficial change on to its descendants.

neutral mutation: Mutation that results in a changed amino acid sequence, but does not alter the protein's function.

nucleotide: One of the structural components, or building blocks, of DNA and RNA. A nucleotide consists of a base (one of four chemicals: adenine, thymine, guanine, and cytosine) plus a molecule of sugar and one of phosphoric acid.

nucleus: Central cell structure that houses the chromosomes.

oligo: Oligonucleotide, short sequence of single-stranded DNA or RNA. Oligos are often used as probes for detecting complementary DNA or RNA because they bind readily to their complements.

oncogene: Gene that is capable of causing the transformation of normal cells into cancer cells.

pedigree: Simplified diagram of a family's geneal ogy that shows family members' relationships to each other and how a particular trait or disease has been inherited.

pharmacogenomics: Study of genetic variation underlying differential response to drugs.

phenotype: Observable traits or characteristics of an organism, for example, hair color, weight, or the presence or absence of a disease. Phenotypic traits are not necessarily genetic.

physical map: Chromosome map of a species that shows the specific physical locations of its genes and/or markers on each chromosome. Physical maps are particularly important when searching for disease genes by positional cloning strategies and for DNA sequencing.

polymerase chain reaction (PCR): Fast, inexpen sive technique for making an unlimited number of copies of any piece of DNA. Sometimes called "molecular photocopying," PCR has had an immense impact on biology and medicine, espe cially genetic research.

polymorphism: Gene that exists in more than one version (allele), and where the rare allele can be found in more than 2 percent of the population.

recessive: Genetic trait that appears only in people who have received two copies of a mutant gene, one from each parent.

restriction enzyme: Enzyme that recognizes spe cific nucleotide sequences in DNA and cuts the DNA molecule at these points.

ribonucleic acid (RNA): Chemical similar to a single strand of DNA. In RNA, the letter U, which stands for uracil, is substituted for T (thymine) in the genetic code. RNA delivers DNA's genetic mes sage to the cytoplasm of a cell where proteins are made.

ribosome: Cellular organelle that is the site of pro tein synthesis.

sequence tagged site (STS): Short DNA segment that occurs only once in the human genome and whose exact location and order of bases are known. Because each is unique, STSs are helpful for chro mosome placement of mapping and sequencing data from many different laboratories. STSs serve as landmarks on the physical map of the human genome.

sex chromosome: One of the two chromosomes that specify an organism's genetic sex. Humans have two kinds of sex chromosomes, one called X and the other Y. Normal females possess two X chromosomes and normal males one X and one Y.

sex-linked: Located on the X chromosome. Sex-linked (or X-linked) diseases are generally seen only in males.

silent mutation: Mutation that results in an unchanged amino acid sequence and thus in a pro tein with normal function.

single-nucleotide polymorphism (SNP): Difference in a single base of DNA.

somatic cell: Any of the body's cells, except the reproductive cells.

suicide gene: Strategy for making cancer cells more vulnerable to chemotherapy. One approach has been to link parts of genes expressed in cancer cells to other genes for enzymes not found in mammals that can convert a harmless substance into one that is toxic to the tumor.

tamoxifen: Drug that, when tested in clinical trials, reduced by about half the development of breast cancer in women taking the drug as compared with women taking a placebo.

transgenic: Experimentally produced organism in which DNA has been artificially introduced and incorporated into the organism's germ line, usually by injecting the foreign DNA into the nucleus of a fertilized embryo.

translocation: Breakage and removal of a large seg ment of DNA from one chromosome, followed by the segment's attachment to a different chromo some.

trisomy: Possessing three copies of a particular chromosome instead of the normal two copies.

tumor suppressor gene: Protective gene that normally limits the growth of tumors. When a tumor suppressor is mutated, it may fail to keep a cancer from growing. *BRCA1* and *p53* are well-known tumor suppressor genes.

vector: Agent that transfers material from one organism to another. For example, a virus can be a vector for the transfer of a gene.

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Masters

Activity 1, *Alike, But Not the Same*

Activity 2, *The Meaning of Genetic Variation*

Activity 3, *Molecular Medicine Comes of Age*

Activity 4, *Are You Susceptible?*

Activity 5, *Making Decisions in the Face of Uncertainty*

An Inventory of a Few Human Traits

How similar are you and your partner? Complete this inventory and compare it with your partner's.

1. number of noses: _____

2. detached earlobes: yes _____ no _____

3. hitchhiker's thumb: yes _____ no _____

4. sex: m _____ f _____

5. dimples: yes _____ no _____

6. middigital hair: yes _____ no _____

7. cross left thumb over right: yes _____ no _____

8. hair color: black _____ dark brown _____ light brown _____
blond _____ red _____ other _____

9. eye color: black _____ brown _____ hazel _____ blue _____ green _____

10. pierced ear or ears: yes _____ no _____

11. wrist circumference: _____ centimeters (to nearest centimeter)

12. allergies: yes _____ no _____

13. height: _____ centimeters (calculate by multiplying the height in inches × 2.5; round off to the nearest 5 centimeters)

Thinking About Human Variation

Work with your partner to answer the following questions.

1. Some human traits can be changed by human intervention and some cannot. Provide examples of each of these types of traits.

2. You probably already know that some traits are genetic and others are environmental. But most human traits reflect an interaction between genetic and environmental factors. Name some traits that might fall into this category and explain why you think they do.

3. Describe some of the benefits of human genetic variation. What are some of the potential problems that it can cause?

How Much Variation?
Beta Globin Gene—Person A

This page contains the DNA base sequence for *part* of a gene called *beta globin*. Hemoglobin, the oxygen carrier in blood, is composed of four polypeptide chains, two alpha polypeptide chains, and two beta polypeptide chains. The *beta globin* gene encodes the amino acid sequence for the beta chain. The complete gene is about 1,700 DNA bases long.

Read the sequence from left to right across the page.

ATG GTG GAC CTG ACT CCT G**A**G GAG AAG TCT GCC GTT ACT GCC CTG TGG GGC AAG GTG
AAC GTG GAT GAA GGT GGT GTT GAG GCC CTG GGC AGGTTGGTATCAAGGTTACAAGACAGGTTTAAG
GAGACCAATAGAAACTGGGCATGTGGAGACAGAGAAGACTCTTGGGTTTCTGATAGGCACTGACTCTCTCTGCCTATT
GGTCTATTTTCCCACCCTTAG G CTG CTG GTG GTC TAC CCT TGG ACC CAG AGG TTC TTT GAG
TCC TTT GGG GAT CTG TCC ACT CCT GAT GCT GTT ATG GGC AAC CCT AAG GTG AAG GCT
CAT GGC AAG AAA GTG CTC GGT GCC TTT AGT GAT GGC CTG GCT CAC CTG GAC AAC CTC
AAG GGC ACC TTT GCC ACA CTG AGT GAG CTG CAC TGT GAC AAG CTG CAC GTG GAT CCT
GAG AAC TTC AGG GTGAGTCTATGGGAC**G**CTTGATGTTTTCTTTCCCCTTCTTTTCTATGGTTAAGTTCATGTC
ATAGGAAGGGGAGAAGTAACAGGGTACAGTTTAGAATGGGAAACAGACGAATGATTGCATCAGTGTGGAAGTCTCA
GGATCGTTTTAGTTTCTTTTATTTGCTGTTCATAACAATTGTTTTCTTTTGTTTAATTCTTGCTTTCTTTTTTTTTCT
TCTCCGCAATTTTTACTATTATACTTAATGCCTTAACATTGTGTATAACAAAAGGAAATATCTCTGAGATACATTAAG
TAACTTAAAAAAAAACTTTACACAGTCTGCCTAGTACATTACTATTTGGAATATATGTGTGCTTATTTGCATATTCAT
AATCTCCCTACTTTATTTTCTTTTATTTTTAATTGATACATAATCATTATACATATTTATGGGTTAAAGTGTAATGTT
TTAATATGTGTACACATATTGACCAAATCAGGGTAATTTTGCATTTGTAATTTTAAAAAATGCTTTCTTCTTTTAATA
TACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTCAGGGCAATAATGATACAATGTATCATGC
CTCTTTGCACCATTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTT
CTGCATATAAATTGTAACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA
TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATGTTCATACCTCTTATCT
TCCTCCCACAG CTC CTG GGC AAC GTG CTG GTC TGT GTG CTG GCC CAT CAC TTT GGC AAA
GAA TTC ATC CCA CCA GTG CAG GCT GCC TAT CAG AAA GTG GTG GCT GGT GTG GCT AAT
GCC CTG GCC CAC AAG TAT CAC TAA GCTCGCTTTCTTGCTGTCCAATTTCTATTAAAGGTTCCTTTGTT
CCCTAAGTCCAACTACTAAACTGGGGGATATTATGAAGGGCCTTGAGCATCTGGATTCTGCCTAATAAAAAACATTTA
TTTTCATTGCAATGATGTATTTAAATTATTTCTGAATATTTTACTAAAAAGGGAATGTGGGAGGTCAGTGCATTTAAA
ACATAAAGAAATGATGAGCTGTTCAAACCTTGGGAAAATACACTATATCTTAAACTCCATGAAAGAA

How Much Variation?
Beta Globin Gene—Person B

This page contains the DNA base sequence for *part* of a gene called *beta globin*. Hemoglobin, the oxygen carrier in blood, is composed of four polypeptide chains, two alpha polypeptide chains, and two beta polypeptide chains. The *beta globin* gene encodes the amino acid sequence for the beta chain. The complete gene is about 1,700 DNA bases long.

Read the sequence from left to right across the page.

ATG GTG GAC CTG ACT CCT G**T**G GAG AAG TCT GCC GTT ACT GCC CTG TGG GGC AAG GTG
AAC GTG GAT GAA GGT GGT GTT GAG GCC CTG GGC AGGTTGGTATCAAGGTTACAAGACAGGTTTAAG
GAGACCAATAGAAACTGGGCATGTGGAGACAGAGAAGACTCTTGGGTTTCTGATAGGCACTGACTCTCTCTGCCTATT
GGTCTATTTTCCCACCCTTAG G CTG CTG GTG GTC TAC CCT TGG ACC CAG AGG TTC TTT GAG
TCC TTT GGG GAT CTG TCC ACT CCT GAT GCT GTT ATG GGC AAC CCT AAG GTG AAG GCT
CAT GGC AAG AAA GTG CTC GGT GCC TTT AGT GAT GGC CTG GCT CAC CTG GAC AAC CTC
AAG GGC ACC TTT GCC ACA CTG AGT GAG CTG CAC TGT GAC AAG CTG CAC GTG GAT CCT
GAG AAC TTC AGG GTGAGTCTATGGGAC**C**CTTGATGTTTTCTTTCCCCTTCTTTTCTATGGTTAAGTTCATGTC
ATAGGAAGGGGAGAAGTAACAGGGTACAGTTTAGAATGGGAAACAGACGAATGATTGCATCAGTGTGGAAGTCTCA
GGATCGTTTTAGTTTCTTTTATTTGCTGTTCATAACAATTGTTTTCTTTTGTTTAATTCTTGCTTTCTTTTTTTTTCT
TCTCCGCAATTTTTACTATTATACTTAATGCCTTAACATTGTGTATAACAAAAGGAAATATCTCTGAGATACATTAAG
TAACTTAAAAAAAAACTTTACACAGTCTGCCTAGTACATTACTATTTGGAATATATGTGTGCTTATTTGCATATTCAT
AATCTCCCTACTTTATTTTCTTTTATTTTTAATTGATACATAATCATTATACATATTTATGGGTTAAAGTGTAATGTT
TTAATATGTGTACACATATTGACCAAATCAGGGTAATTTTGCATTTGTAATTTTAAAAAATGCTTTCTTCTTTTAATA
TACTTTTTTGTTTATCTTATTTCTAATACTTTCCCTAATCTCTTTCTTTCAGGGCAATAATGATACAATGTATCATGC
CTCTTTGCACCATTCTAAAGAATAACAGTGATAATTTCTGGGTTAAGGCAATAGCAATATTTCTGCATATAAATATTT
CTGCATATAAATTGTAACTGATGTAAGAGGTTTCATATTGCTAATAGCAGCTACAATCCAGCTACCATTCTGCTTTTA
TTTTATGGTTGGGATAAGGCTGGATTATTCTGAGTCCAAGCTAGGCCCTTTTGCTAATCATGTTCATACCTCTTATCT
TCCTCCCACAG CTC CTG GGC AAC GTG CTG GTC TGT GTG CTG GCC CAT CAC TTT GGC AAA
GAA TTC ATC CCA CCA GTG CAG GCT GCC TAT CAG AAA GTG GTG GCT GGT GTG GCT AAT
GCC CTG GCC CAC AAG TAT CAC TAA GCTCGCTTTCTTGCTGTCCAATTTCTATTAAAGGTTCCTTTGTT
CCCTAAGTCCAACTACTAAACTGGGGGATATTATGAAGGGCCTTGAGCATCTGGATTCTGCCTAATAAAAAACATTTA
TTTTCATTGCAATGATGTATTTAAATTATTTCTGAATATTTTACTAAAAAGGGAATGTGGGAGGTCAGTGCATTTAAA
ACATAAAGAAATGATGAGCTGTTCAAACCTTGGGAAAATACACTATATCTTAAACTCCATGAAAGAA

How Much Variation?
Doing the Math

Calculate the amount of variation in the DNA in the *beta globin* gene between person A and person B. If you need help, use the example below as a guide.

1. How many bases are different between the sequence shown for person A and the sequence shown for person B? _____

   How many total bases are in the sequence? _____ (Your teacher will give you this number.)

   Divide the number of different bases by the total number of bases in the sequence.

   $$\frac{\text{number of different bases}}{\text{total number of bases}} = \_\_\_\_\_ = \_\_\_\_\_$$

2. The percentage difference is _____ × 100 = _____ %.

3. The human genome has about 3 billion bases. Assume that the degree of difference you just calcu lated applies across the entire genome. How many total base differences would you expect to find between person A and person B?

   3,000,000,000 × _____ = _____ total differences

   or, in scientific notation, $3 \times 10^9 \times$ _____ = _____

Example

The sophomore class at Roosevelt High School in Metropolitan City is one of five high schools that conduct two community service projects each year, one in the fall and one in the spring. This fall, 150 students from Roosevelt High signed up to help. The same number signed up in the spring, but 30 of the students were different. What percentage of the students was different between the fall group and the spring group?

1. To calculate the percentage difference, first divide the number of different students in the spring by the total number of students in the group:

   $$\frac{\text{number of different students}}{\text{total number of students}} = \frac{30}{150} = .2$$

2. Convert this result to a percentage by multiplying by 100: .2 × 100 = 20%

3. The sophomore classes at all five high schools combined include about 3,000 students. Assume that the degree of difference between the students who signed up for the community service projects in the fall and spring across all five high schools is the same as it was at Roosevelt High. How many different students would you expect to find in total between the fall and spring projects?

   3,000 × 20% = 600 different students

Exploring Sickle Cell Disease

Imagine that you are a family practice physician and that an African-American woman, Audrey Lindsey, and her family are your patients. Just before her twins, Sondra and Jason, were born, Ms. Lindsey's hus band, also African-American, died in an automobile accident. His parents were physiologically normal, but he had a brother who died of sickle cell disease at the age of 19. Ms. Lindsey explains to you that it is important to her to know whether her twins carry the allele associated with sickle cell disease.

1. Study the minidocumentary *What Is Sickle Cell Disease?* on the CD-ROM. Use the *Reference Database* (also on the CD-ROM) and any other resources that are available to you (for example, your textbook) to answer the following questions:

   a. What are the primary symptoms of sickle cell disease? What happens in a person's body to cause these symptoms?

   b. How is Hb S (sickle hemoglobin) different from Hb A (normal hemoglobin)?

   c. How can this difference in hemoglobin be detected in the laboratory?

   d. What does this difference in hemoglobin tell you about the DNA of people whose cells make Hb S as compared with people whose cells make normal hemoglobin?

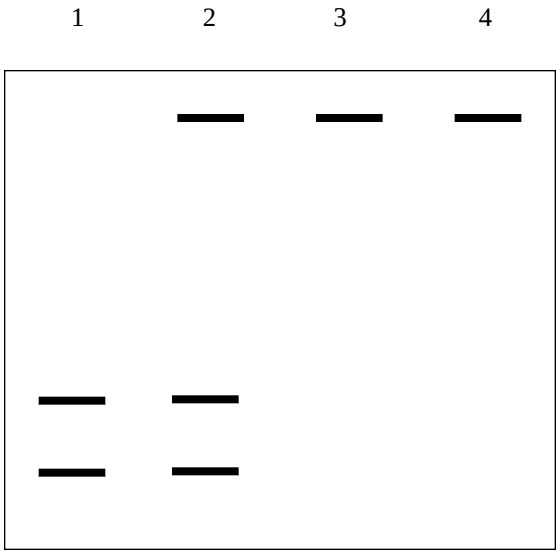
   e. What is the difference between sickle cell disease and sickle cell trait? Demonstrate in your answer that you understand how sickle cell disease is inherited.

2. Use what you learned about sickle cell disease and trait to propose a way to determine whether Ms. Lindsey's twins have sickle cell trait. Explain your procedure to your teacher, then use the informa tion provided on the handout your teacher will give you to determine the results of the test.

3. Write the dialogue for a brief (2–3 minute) scene in which you explain to Ms. Lindsey the results of the tests you ran on the twins, what these results say about the inheritance of the sickle cell trait in her family, and the implications of your findings for the twins' health.

Results of the Lindsey Test

Examine the following results to determine Sondra‘s and Jason’s status with respect to sickle cell trait.



Lane

1 Standard—DNA from allele for Hb A

2 DNA from Sondra Lindsey

3 DNA from Jason Lindsey

4 Standard—DNA from allele for Hb S

Molecular Medicine Comes of Age

One of the benefits of understanding human genetic variation at a molecular level is its practical value for helping us understand and combat disease.

Saving Firm A
Role: Team Coordinator

You are an experienced executive for Firm A, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. Although you worked in a research lab years ago, your assignments have changed across the years. Now, you head up a small team of scientists and biostatisti cians.* The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You receive an e-mail from Firm A's vice president for research. The e-mail asks your team to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you decide to call a team meeting for the next day. To prepare for the meeting, you study the relevant section of the e-mail closely.

> . . . Drug X is a bronchodilator. That is, it opens up the breathing passages in the lungs, providing relief for people who have asthma attacks. Drug X has been tested with an initial set of 270 children for its effectiveness in alleviating wheezing symp toms associated with asthma. The results were incon clusive. Some of the children showed significant improvement when they took the drug. Other children showed little or no relief.
>
> What's going on here? Can you find a pattern in the data that will help us understand how the drug is acting? To make this drug marketable, we need to define exactly when or with whom the drug is likely to be effective. If we can't, physicians will have no reason to prescribe it over another drug.

*A biostatistician is trained in biology and statistical analysis. Biostatisticians are experts in the experimental designs and statistical methods that are most helpful in conducting research in biology and medicine.

Saving Firm A
Role: Physiologist

You are an experienced physiologist* for Firm A, a U.S.-based company that develops, tests, manufac tures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists and biosta tisticians.** The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been reading a research report in your office. Now, your assistant calls to say that the leader of your team has called a special team meeting to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you are not surprised your team leader has called this meeting. You don't know much about the condition the drug is intended to treat. You pull out a medical textbook to learn more about it.

Asthma

Asthma is a condition in which the smooth muscle inside the bronchioles (small tubes within the lungs) contracts abnormally. This causes the victim to have difficulty breathing. Asthma occurs in 3 to 5 percent of all people at some time in their lives. It usually is caused by an allergic reaction to foreign substances in the air, for example, pollen, dust, or pet hair.

People suffering from asthma typi cally are treated with drugs called bron chodilators. These substances expand the bronchioles and alleviate the abnormal contractions, making breathing easier. Most bronchodilators work by binding (attaching) to and stimulating specific receptors on the cells of the smooth mus cle in the lungs. This causes the muscles to relax and the bronchioles to expand.

*A physiologist studies the basic processes of life, such as respiration, digestion, circulation, or cellular metabolism.

**A biostatistician is trained in biology and statistical analysis. Biostatisticans are experts in the experimental designs and statistical methods that are most helpful in conducting research in biology and medicine.

Saving Firm A
Role: Molecular Biologist

You are an experienced molecular biologist* who works for Firm A, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scien tists and biostatisticians.** The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

Your assistant has left you a note. It says that the leader of your team has called a special team meeting to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you are not surprised that your team leader is taking this problem so seriously. You pick up a scientific article and decide to spend the rest of the afternoon studying it.

. . . Scientists at Elvan-Ray, a pharmaceutical company that makes an important drug for treating Alzheimer disease, have reported some new research results. There are three variants of a gene called "ApoE" (pro nounced A-poh-ee). The three variants are: E2, E3, and E4. The particular gene variants that a person inherits affect his or her risk of developing Alzheimer disease. They also affect his or her response to the drug. In this study, people with particuliar variants of the gene (non-E4 ver sions of the gene) responded very well to the drug. People with a different variant (the E4 type of the gene) eventually got worse, even though they were taking the drug.

The article includes a table showing the response to the drug based on the patients' genotype:

Response to Drug Z by Alzheimer Genotype

Genotype, Based on ApoE Type	Improvement After Administration of Drug Z			
	None	Low	Moderate	High
E2/E2[1]				X
E3/E3[2]			X	
E4/E4[1]	X			

[1] These genotypes are uncommon.
[2] This genotype is common.

*A molecular biologist studies the structures and processes of life at the molecular level. Molecular biologists investi gate such things as the structure of proteins and DNA and how these molecules regulate cellular activities.

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Saving Firm A
Role: Biostatistician

You are an experienced biostatistician* who works for Firm A, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists and biostatisticians. The team provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been analyzing a new set of test results that one of those larger teams just sent you. Now, your assistant comes into your office to say that the leader of your team has called a special team meeting. The objective is to evaluate a problem the company is having with one of the drugs it is developing. Because of the importance of this drug to the company's future, you are not surprised that your team leader is tak ing this problem so seriously. You decide you'd better learn something about the problem before the meet ing. Using the company's computerized database, you call up the test results on the drug and study them carefully.

CONFIDENTIAL

Do not discuss or circulate these data outside Firm A.

Preliminary Results of a Study of 300 Children Treated with Drug X for Wheezing Associated with Asthma

Number of Subjects and Extent of Relief After Administration of Drug X

Response to Drug X			
Sex	**Significant Relief**	**Some Relief**	**Little Relief**
female	51 = ___%	64 = ___%	35 = ___%
male	51 = ___%	64 = ___%	35 = ___%
total	102	128	70
Pet Dander in the Home#	**Significant Relief**	**Some Relief**	**Little Relief**
pets	40 = ___%	52 = ___%	28 = ___%
no pets	62 = ___%	76 = ___%	42 = ___%
total	102	128	70

#Pet dander is tiny particles of hair, skin, or feathers that can cause an allergic reaction like asthma.

Calculate the percentages and insert them where indicated in the table. To calculate a percentage, divide the number of subjects in any category by the total number of subjects in that column. Then, multiply the result by 100. For example, for the data on "pet dander in the home," 40 people exposed to pet dander at home had "significant relief," and the total number of subjects in the "significant relief" column is 102. Thus, $40 / 102 = .39 \times 100 = 39\%$ of the people had significant relief.

*A biostatistician is trained in biology and statistical analysis. Biostatisticians are experts in the experimental designs and statistical methods that are most helpful in conducting research in biology and medicine.

Report Form for Firm A

Use this form to organize your discussion about Drug X and report your team's results. You and your teammates will have 30 minutes to complete this form. Be prepared to explain your analysis and proposed solution to the rest of the class.

1. What is the biological problem facing Firm A with respect to Drug X?

2. Describe asthma in your own words (refer to the *Team Coordinator* and *Physiologist* handouts).

3. What is Drug X designed to do for asthma sufferers (refer to the *Team Coordinator* and *Physiologist* handouts)?

4. Look at the preliminary test results (refer to the *Biostatistician* handout). Can you predict which group will be helped most or least by Drug X? For example, does the sex of an individual make a difference? Does having pets make a difference? Explain your answers.

5. What does the example of ApoE (refer to the *Molecular Biologist* handout) suggest might be happen ing with Drug X? Based on this example, what might Firm A investigate?

6. Firm A's vice president for research (your teacher) will provide you with some new data. What do the new data reveal about Drug X?

7. What would be an appropriate way to prescribe Drug X?

8. Has your team solved the biological problem facing the company with respect to Drug X? What new problems has it raised?

Some New Genetic Data (Firm A)

CONFIDENTIAL

Do not discuss or circulate these data outside Firm A.

Preliminary Results of a Study of 300 Children Treated with Drug X for Wheezing Associated with Asthma

Number of Subjects and Extent of Relief by Genotype

	Response to Drug X		
Genotype, as Indicated by Amino Acids*	**Significant Relief**	**Some Relief**	**Little Relief**
arginine/arginine	80 (78%)	20 (16%)	8 (11%)
arginine/glycine	20 (20%)	100 (82%)	24 (35%)
glycine/glycine	2 (2%)	2 (2%)	38 (54%)
total	102	122	70

*Molecular biologists have determined that a particular protein acts as a receptor for Drug X. As shown in the left-hand column, variations in the gene that encodes this receptor protein cause different amino acids to be located at position (number) 16 in the protein. There are two amino acids listed (for example, argi nine / arginine) because each person has inherited two genes that encode the receptor protein.

Saving Firm B
Role: Team Coordinator

You are an experienced executive for Firm B, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. Although you worked in a research lab years ago, your assign ments have changed across the years. Now, you head up a small team of scientists that provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You receive an e-mail from Firm B's vice president for research with a new assignment for your team. Although one of the company's major products is still doing very well in the marketplace, the vice presi dent wants to be sure that the company keeps its competitive edge in this area. Because of the importance of this product to the company's well-being, you decide to call a team meeting for the next day. To prepare for the meeting, you study the relevant section of the e-mail closely.

> . . . As you know, Drug Y, a treatment for cystic fibrosis, is our company's primary product. . . .
>
> I'd like your team to spend some time identifying possible new directions we could go in developing new drugs for the treatment of this disease. Much has been learned about cystic fibrosis in the last few years. Does any of this new information suggest some different approaches we could take to treating the disease? Ideally, we could develop one or two new drugs that would supplement, or even one day replace, Drug Y as our company's major product.

Saving Firm B
Role: Physiologist

You are an experienced physiologist* for Firm B, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists that provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been reading a research report in your office. Now, your assistant calls to say that the leader of your team has called a special team meeting to do some brainstorming about new approaches the company could take in developing drugs for the treatment of cystic fibrosis. You know that Drug Y, your company's major product, is widely used as a treatment for this disease. Still, a lot has been learned about cystic fibro sis in the last few years. If the company is to maintain its competitive edge, it needs to keep looking for new, more effective treatments. You don't know much about cystic fibrosis, so you pull out a medical text-book to learn more about it.

Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disease that affects approximately 30,000 children and young adults in the United States. CF affects tissues that produce mucus secretions, such as the airway, the gastroin testinal tract, and the ducts of the pancreas. CF causes the body to produce an abnormally thick, sticky mucus that clogs these passages. The most characteristic symptom of CF is the excessive pro duction of mucus in the airways and lungs. This mucus provides an ideal breeding ground for many microorganisms, and CF patients have fre quent airway infections that can require hospitiliza tion and even cause death. Thick mucus also clogs the pancreatic ducts and prevents enzymes from the pancreas from reaching the intestines to help digest food.

People with CF have many symptoms. The most common are very salty sweat; frequent coughing, wheezing, and pneumonia; and an excessive appetite, but poor weight gain and slowed growth and development.

*A physiologist studies the basic processes of life, such as respiration, digestion, circulation, or cellular metabolism.

Saving Firm B
Role: Molecular Biologist

You are an experienced molecular biologist* for Firm B, a U.S.-based company that develops, tests, manu factures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists that pro vides expert advice to the much larger teams that actually design, develop, and test new drugs.

Your assistant has left you a note. It says that the leader of your team has called a special team meeting to do some brainstorming about new approaches the company could take in developing drugs for the treat ment of cystic fibrosis. You know that Drug Y, your company's major product, is widely used as a treat ment for this disease. Still, if the company is to maintain its competitive edge, it needs to keep looking for new, more effective treatments. You decide to find out what the latest research says about CF, and you pick up a recent article.

. . . In 1989, researchers at the University of Michigan and at the Hospital for Sick Children in Toronto, Canada, identified the genetic defect responsible for CF. Mutations in one gene, called the cystic fibrosis trans-membrane conductance regu-lator (CFTR) cause the body to make nonfunctional CFTR protein. The normal CFTR protein is embedded in the cell membranes of several types of cells in the body, where it acts as a "channel" that opens and closes to control the movement of chloride ions out of the cells. Depending on the specific type of CF muta tion a patient has, the CTFR protein may be reduced in quantity or missing, or it may be present but not work properly . . .

As you read, you develop a flow chart of the biological effects of the most common CF mutation:

1. A person inherits two mutated genes for the CFTR protein.

↓

2. These mutations result in one missing amino acid in the CFTR protein that his or her cells make.

↓

3. The absence of this amino acid means that the CFTR protein in his or her cells does not fold into its proper shape.

↓

4. Most of this improperly folded CFTR protein is destroyed before it can be inserted into the cell membrane.

↓

5. The absence of properly functioning CFTR protein in the cell membrane leads to abnormal movement of chloride ions and water in and out of the cell.

↓

6. The result of this abnormal movement of chloride ions and water is the production of thick, sticky mucus.

↓

*A molecular biologist studies the structure and processes of life at the molecular level. Molecular biologists are inter ested in such things as the structure and function of proteins and DNA and the molecular mechanisms that regulate activities inside the cell.

Saving Firm B
Role: Physician

You are an experienced physician for Firm B, a U.S.-based company that develops, tests, manufactures, and distributes pharmaceuticals worldwide. You are part of a small team of scientists that provides expert advice to the much larger teams that actually design, develop, and test new drugs.

You have been analyzing a new set of test results that one of those larger teams just sent you. Now, your assistant comes into your office to say that the leader of your team has called a special team meeting to do some brainstorming about new approaches the company could take in developing drugs for the treatment of cystic fibrosis. You know that Drug Y, your company's major product, is widely used as a treatment for this disease. Still, a lot has been learned about cystic fibrosis in the last few years. If the company is to maintain its competitive edge, it needs to keep looking for new, more effective treatments. You decide that you will prepare for the meeting by learning more about Drug Y and also by learning about other compa nies' products to treat cystic fibrosis. You pull out some reference material and learn that improvements in treatment across the past few years have increased the average survival time of patients with CF from under 5 years to approximately 30 years. You create a table to help you organize what you learn about these treatments, but leave the last column blank in order to discuss it with your teammates.

Summary of Existing Treatment Approaches for CF

Major Type	Description	Primary Benefit	Treatment Addresses Symptoms or Cause?
chest physical therapy	vigorous tapping on the back and chest with cupped hands	dislodges mucus from lungs, allowing better breathing and reducing the risk of infection	
antibiotics	antibiotics administered intravenously, through pills, or, in the case of Drug Y, as a medicated vapor that is inhaled	treats lung infections that can damage the lungs and even cause death	
enzyme supplements	supplements of pancreatic enzymes	improves digestion	
diet	enriched diet and supple-ments of vitamins and other nutrients	reduces malnutrition and improves growth and development	

Report Form for Firm B

Use this form to organize your discussion about Drug Y and report your team's results. You and your teammates will have 30 minutes to complete this form. Be prepared to explain your analysis and proposed solution to the rest of the class.

1. What is the problem facing Firm B with respect to Drug Y (refer to the *Team Coordinator* handout)?

2. Describe cystic fibrosis in your own words (refer to the *Physiologist* handout).

3. What have we learned in the past few years about the cause of CF (refer to the *Molecular Biologist* handout)?

4. What is Drug Y (and most other current treatments) designed to do for CF patients (refer to the *Physician* handout and discuss what goes in the last column of the table provided)?

5. Firm B's vice president for research (your teacher) will provide you with some new information. What clue does this new information provide about how Firm B might approach developing new treatments for CF?

6. What new approaches do you recommend Firm B consider as it attempts to design and develop one or more new treatments for CF?

7. Has your team solved the problem facing the company with respect to Drug Y? What new problems has it raised?

Some New Information (Firm B)

INTEROFFICE-

TO: Team Investigating New Treatment Approaches for Cystic Fibrosis

FROM: Vice-President for Research, Firm B

CONFIDENTIAL

Do not discuss or circulate this memo outside Firm B.

I just heard from a colleague that another research team (not associated with our com pany) will apply soon for a patent on a new method for treating cystic fibrosis. These researchers have spent years studying exactly what goes wrong in CF cells. The new method they will propose involves using small fragments of a protein normally found in brain cells to create working chloride channels in CF cells that lack such channels. Does this offer us any clues about how we might change our treatment approach to CF? Are there any other places in the flow chart of biological effects of CF where we could intervene to correct the problems in CF cells?

Rolling the Dice

Imagine that you are going to live your entire life—your teen years, your adult years, and your senior cit izen years—in the next 10 minutes and that your choices in life are going to be made by a roll of the dice. Begin with your teen years and roll one die to discover your behavioral choices in each category for each life stage. Use the information provided to determine how many points you receive for each behavior. Record the result in the blanks provided.

By the way, the object of this game is to stay alive to a ripe old age. You do this by keeping your "heart points" below the threshold level of 85. Once you exceed 85 points at any life stage, you're out (you've had a fatal heart attack).

Life Stage 1: Choices as a Teenager **Heart Points**

1. Diet. Roll one die. If you rolled:

1 or 2	You eat a well-balanced, low-fat diet (subtract 10 points).	_____
3 or 4	You eat some high-fat fast food and junk food (add 5 points).	_____
5 or 6	You eat a lot of high-fat fast food and junk food (add 10 points).	_____

2. Exercise. Roll the die again. If you rolled:

1 or 2	You're a couch potato! You get little or no exercise beyond walking from the TV to the refrigerator (add 15 points).	_____ _____
3 or 4	You get a moderate amount of exercise (subtract 5 points).	_____
5 or 6	You exercise regularly (subtract 15 points).	_____

3. School/Job/Relationships. Roll the die again. If you rolled:

1	You feel that your life is pretty stress free (subtract 10 points).	_____
6	You are under a great deal of stress at home, at school, and at work (add 10 points).	_____
For any other rolls, add no points.		_____

4. Smoking. Roll the die again. If you rolled:

1 or 2	You don't smoke and are rarely exposed to those who do (subtract 20 points).	_____
3 or 4	You don't smoke, but you are around many people who smoke (add 10 points).	_____
5 or 6	You smoke one or more packs of cigarettes a day (add 20 points).	_____

Total risk points from choices made as a teenager: _____

If the total is more than 85, you've had a fatal heart attack.

Life Stage 2: Choices as an Adult (Ages 20–50)

(Start from zero points.)

1. Diet. Roll one die. If you rolled:

1 or 2	You eat a well-balanced, low-fat diet (subtract 10 points).	_____
3 or 4	You eat some high-fat fast food and junk food (add 5 points).	_____
5 or 6	You eat a lot of high-fat fast food and junk food (add 10 points).	_____

2. Exercise. Roll the die again. If you rolled:

1 or 2	You're a couch potato! You get little or no exercise beyond walking from the TV to the refrigerator (add 20 points).	_____
3 or 4	You get a moderate amount of exercise (subtract 5 points).	_____
5 or 6	You exercise regularly (subtract 15 points).	_____

3. Job/Relationships. Roll the die again. If you rolled:

1	You feel that your life is pretty stress free (subtract 10 points).	_____
6	You are under a great deal of stress at home and at work (add 10 points).	_____

For any other rolls, add no points.

4. Smoking. Roll the die again. If you rolled:

1 or 2	You started smoking during your teen years (add 20 points).	
	You did not start smoking during your teen years (add no points).	_____
3 or 4	You smoked during your teen years, but you have stopped smoking (subtract 20 points).	_____
	You did not smoke during your teen years (subtract 5 points).	_____
5 or 6	You smoke one or more packs of cigarettes a day (add 20 points).	_____

Total risk points from choices made as an adult: _____

Total risk points from choices made as a teenager: _____

Total Points _____

If the total is more than 85, you've had a fatal heart attack.

Life Stage 3: Choices as a Senior Citizen (Over Age 50)

(Start from zero points.)

1. Diet. Roll one die. If you rolled:

1or 2	You eat a well-balanced, low-fat diet (subtract 10 points).	_____
3 or 4	You eat some high-fat fast food and junk food (add 5 points).	_____
5 or 6	You eat a lot of high-fat fast food and junk food (add 10 points).	_____

2. Exercise. Roll the die again. If you rolled:

1 or 2	You're a couch potato! You get little or no exercise beyond walking from the TV to the refrigerator (add 20 points).	_____
3 or 4	You get a moderate amount of exercise (subtract 5 points).	_____
5 or 6	You exercise regularly (subtract 15 points).	_____

3. Retirement/Relationships. Roll the die again. If you rolled:

1	You feel that your life is pretty stress free (subtract 10 points).	_____
5 or 6	You are under a great deal of stress (add 10 points).	_____

For any other rolls, add no points.

4. Smoking. Roll the die again. If you rolled:

1 or 2	You smoked before, but you stopped smoking (subtract 20 points).	_____
	You did not smoke before (subtrat no points).	_____
3, 4, 5, or 6	You started smoking as a teenager or an adult (add 20 points).	_____
	You did not start smoking as a teenager or an adult or you stopped smoking as an adult (add no points).	_____

Total risk points from choices made as a senior citizen: _____

Total risk points from choices made as an adult: _____

Total risk points from choices made as a teenager: _____

Total Points _____

If the total is more than 85, you've had a fatal heart attack.

Thinking About the Game

Complete the following steps to compare the results of the game with and without considering genetic factors.

1. Transfer your heart points from *Rolling the Dice* into the left-hand column below.
2. Your relevant genes envelope contained heart points related to your genetic risk. Enter that number in the right-hand column below and recalculate your total points for each life stage.

Review - Risk from Behavioral Choices Only		**Recalculate - Risk from Genes and Choices**	
		Relevant genes	_____
Life Stage 1: Teen years	_____	Life Stage 1: Teen years	+_____
		Subtotal	_____
Life Stage 2: Adult years	+_____	Life Stage 2: Adult years	+_____
Subtotal	_____	Subtotal	_____
Life Stage 3: Senior citizen years	+_____	Life Stage 3: Senior citizen years	+_____
Total	_____	Total	_____

3. Remember, if you exceeded 85 points in any life stage, you have had a fatal heart attack. What effect did including your points for genetic risk have on your outcome?

4. Think about the behavioral choices you made in each life stage.

   a. Did everyone make the same choices?

   b. Were all of the choices equally risky?

   c. Were the risk factors associated with the choices reversible?

   d. Were the choices under personal control?

5. Now, think about the effects of the genetic risk factors in each life stage.

   a. Does everyone have the same genes?

   b. Did all of the genetic factors have the same effect?

   c. Were the genetic factors reversible or under personal control?

6. Assume that genetic testing showed that you were at increased risk for a fatal heart attack 20 years from now. Would you want to know? Why or why not? Would that information cause you to change your behavior? If not, what kind of information or event would cause you to change your behavior?

7. We know about only a few genes that affect the likelihood of a heart attack, and we have the ability to test for even fewer of them. In the future, we certainly will learn about more of these genes. How will an increased knowledge of the genetic factors associated with heart disease have a positive impact on individuals and society? How will it have a negative impact?

8. Our ability to detect genetic variations that are related to common diseases likely will improve. How might that ability shift some of the responsibility for health care from physicians to individuals?

High Genetic Risk

High Genetic Risk

You have a parent or sibling who had a fatal heart attack.

ADD 40 HEART POINTS.

High Genetic Risk

You have a parent or sibling who had a fatal heart attack.

ADD 40 HEART POINTS.

High Genetic Risk

You have a parent or sibling who had a fatal heart attack.

ADD 40 HEART POINTS.

High Genetic Risk

You have a parent or sibling who had a fatal heart attack.

ADD 40 HEART POINTS.

Moderate Genetic Risk

Moderate Genetic Risk

You have an aunt or uncle who had a fatal heart attack.

ADD 10 HEART POINTS.

Moderate Genetic Risk

You have an aunt or uncle who had a fatal heart attack.

ADD 10 HEART POINTS.

Moderate Genetic Risk

You have an aunt or uncle who had a fatal heart attack.

ADD 10 HEART POINTS.

Moderate Genetic Risk

You have an aunt or uncle who had a fatal heart attack.

ADD 10 HEART POINTS.

Low Genetic Risk

Low Genetic Risk

There is no history of fatal heart attacks among your close relatives.

ADD NO HEART POINTS.

Low Genetic Risk

There is no history of fatal heart attacks among your close relatives.

ADD NO HEART POINTS.

Low Genetic Risk

There is no history of fatal heart attacks among your close relatives.

ADD NO HEART POINTS.

Low Genetic Risk

There is no history of fatal heart attacks among your close relatives.

ADD NO HEART POINTS.

Genetic Protection

Genetic Protection

You have high HDL cholesterol levels.-

SUBTRACT 10 HEART POINTS.-

BUT IF YOU SMOKE, SUBTRACT NO POINTS.-

Genetic Protection

You have high HDL cholesterol levels.-

SUBTRACT 10 HEART POINTS.-

BUT IF YOU SMOKE, SUBTRACT NO POINTS.-

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Genetic Protection

You have high HDL cholesterol levels.-

SUBTRACT 10 HEART POINTS.-

BUT IF YOU SMOKE, SUBTRACT NO POINTS.-

Analyzing the Issues

Use this worksheet to take notes while you watch the video *Making Decisions in the Face of Uncertainty* a second time. List any questions that occur to you. Be prepared to discuss these questions at the time your teacher indicates.

Segment 1: Considering the Test

1. What decision does Beth have to make?

2. Who might be affected by Beth's decision?

3. What arguments support having the test?

4. What arguments support *not* having the test?

5. What factors do you think Beth and Charlie should consider in making their decisions?

Segment 2: A Family Question

1. What new facts have you learned about breast cancer?

2. What are some of the family issues that arise in this counseling session?

3. What reasons does the genetic counselor give for not testing Jennifer? Do you agree that children under 18 should not be tested?

4. Beth's mother says, "I'm not sure more information is better." Do you agree with her? Explain your answer.

Segment 3: The Test Results

1. Beth and her mother have had the genetic test. What new information have we learned?

Segment 4: A Diagnosis of Breast Cancer

1. What new information have we learned about Beth?

2. What major decisions do Beth and her husband discuss in this segment?

3. What do you think Beth and Charlie should do? Why?

Segment 5: Jennifer's Decision

1. What new information emerges in this segment?

2. What is Jennifer's primary concern about the test?

3. Do you think employers or insurers should be able to deny employment or insurance to a person who has a genetic predisposition to a disease such as cancer? Explain your position.