Human Genetic Variation

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National Institutes of Health

U.S. Department of Health and Human Services
National Institutes of Health
National Human Genome Research Institute

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Foreword

This curriculum supplement, from the NIH Curriculum Supplement Series, brings cutting-edge medical science and basic research discoveries from the laboratories of the National Institutes of Health (NIH) into classrooms. As the largest medical research institution in the United States, NIH plays a vital role in the health of all Americans and seeks to foster interest in research, science, and medicine-related careers for future generations. NIH’s Office of Science Education is dedicated to promoting scientific literacy and the knowledge and skills we need to secure a healthy future for all.

We designed this curriculum supplement to complement existing life science curricula at both the state and local levels and to be consistent with the National Science Education Standards.1 It was developed and tested by a team of teachers, scientists, medical experts, and other professionals with relevant subject-area expertise from institutes and medical schools across the country, representatives from the National Human Genome Research Institute, and curriculum design experts from Biological Sciences Curriculum Study (BSCS) and Videodiscovery, Inc. The authors incorporated real scientific data and actual case studies into classroom activities. A three-year development process included geographically dispersed field tests by teachers and students. For the 2011 (third) printing, key sections of the supplement were updated, but the Student Lessons remain basically the same.

The curriculum supplements enable teachers to facilitate learning and stimulate student interest by applying scientific concepts to real-life scenarios. Design elements include a conceptual flow of lessons based on the BSCS 5E Instructional Model (page 3), cutting-edge science content, and built-in assessment tools. Activities promote active and collaborative learning and are inquiry-based to help students develop problem-solving strategies and critical-thinking skills.

Each of our curriculum supplements comes with a complete set of materials for teachers, including extensive background and resource information, detailed lesson plans, masters for student worksheets, and a Web site with videos, interactive activities, updates, and corrections (as needed). The supplements are distributed at no cost to educators across the United States upon request. They may be copied for classroom use but may not be sold.

We welcome your comments. For a complete list of curriculum supplements and ordering information, or to submit feedback, please visit http://science.education.nih.gov or write to

Curriculum Supplement Series
Office of Science Education
National Institutes of Health
6100 Executive Boulevard, Suite 3E01
Bethesda, MD 20892-7520

We appreciate the valuable contributions of the talented staff at BSCS and Videodiscovery, Inc. We are also grateful to the NIH scientists, advisors, and all other participating professionals for their work and dedication. Finally, we thank the teachers and students who participated in focus groups and field tests to ensure that these materials are both engaging and effective.

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
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1 The National Academy of Sciences released the National Science Education Standards in 1996, outlining what all citizens should understand about science by the time they graduate from high school. The Standards encourages teachers to select major science concepts or themes that empower students to use information to solve problems rather than stressing memorization of unrelated information.
About the National Institutes of Health

Founded in 1887, NIH is the federal focal point for health research in the United States. Today, NIH is one of the agencies within the Department of Health and Human Services. Its mission is science in pursuit of fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability. NIH works toward meeting the mission by providing leadership, direction, and grant support to programs designed to improve the health of the nation through research.

NIH's education programs contribute to ensuring the continued supply of well-trained basic research and clinical investigators, as well as the myriad professionals in the many allied disciplines who support the research enterprise. These efforts also help educate people about scientific results so that they can make informed decisions about their own—and the public's—health.

This curriculum supplement is one such education effort. It is a collaboration among the National Human Genome Research Institute, the NIH Office of Science Education, Biological Sciences Curriculum Study, and Videodiscovery, Inc.

For more about NIH, visit http://www.nih.gov.
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 20,000 to 25,000 genes that orchestrate a single cell’s development into a human infant and then into 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 set the year 2005 as its deadline for completing the DNA sequence of the human genome, our genetic blueprint. On April 14 of 2003, NHGRI, the Department of Energy, and their partners around the world announced the successful completion of the Human Genome Project.

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 will also likely 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.genome.gov.
Headquartered in Colorado Springs, Colorado, BSCS was founded in 1958 as a curriculum study committed to an evidence- and inquiry-based approach to science education. BSCS instructional materials and professional development services are based on current research about teaching and learning for all science classrooms, kindergarten through college.

BSCS's materials are extensively field-tested in diverse settings across the country and evaluated for proven effectiveness. The BSCS 5E Instructional Model and inquiry are hallmarks of its materials, placing students at the center of their learning.

The BSCS mission is to transform science teaching and learning through research and development that strengthens learning environments and inspires a global community of scientifically literate citizens. BSCS is a 501(c)(3) nonprofit organization.

For more information, please visit http://www.bscs.org.
Introduction to Human Genetic Variation

This module 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 6.9 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 knowledge that scientists gained as they sequenced the human genome is 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, students will have the chance to think about how the detailed analysis of human genetic variation is already changing their 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 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—the members of any given species are actually 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 called this view population thinking, and it pervades modern biology.

Darwin, however, even while working as Gregor 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.

**Figure 1.** Humans are a genetically diverse lot. How will understanding this diversity at the molecular level change our lives?
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 improved diagnosis, prevention, and treatment of disease.
• Our growing understanding of human genetic variation will allow us to identify genes 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 module's five lessons will be effective vehicles for carrying 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 lesson are intended to focus the students' attention on those concepts as the lesson draws to a close.
Implementing the Module

The five lessons 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 lesson.

What Are the Goals of the Module?

*Human Genetic Variation* is designed to help students reach the following major goals associated with biological literacy:

- to understand a set of basic scientific principles related to human genetic variation,
- to experience the process of inquiry and develop an enhanced understanding of the nature and methods of science, and
- to recognize the role of science in society and the relationship between basic science and personal and public health.

What Are the Science Concepts and How Are They Organized?

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.

<table>
<thead>
<tr>
<th>Lesson</th>
<th>Learning Phase</th>
<th>Major Concepts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesson 1</strong>&lt;br&gt;<em>Alike, But Not the Same</em></td>
<td>Engage</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Lesson 2</strong>&lt;br&gt;<em>The Meaning of Genetic Variation</em></td>
<td>Explore</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Lesson 3</strong>&lt;br&gt;<em>Molecular Medicine Comes of Age</em></td>
<td>Explain</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Lesson 4</strong>&lt;br&gt;<em>Are You Susceptible?</em></td>
<td>Elaborate</td>
<td>Studying the genetic and environmental factors involved in multifactorial diseases will lead to increased diagnosis, prevention, and treatment of disease.</td>
</tr>
<tr>
<td><strong>Lesson 5</strong>&lt;br&gt;<em>Making Decisions in the Face of Uncertainty</em></td>
<td>Evaluate</td>
<td>Our growing understanding of human genetic variation will allow us to identify genes 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.</td>
</tr>
</tbody>
</table>
Human Genetic Variation

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 (Making Decisions in the Face of Uncertainty). Table 1 summarizes the sequence of major concepts addressed by the five lessons.

Although we encourage you to use the lessons in the sequence outlined in Table 1, many of the lessons can be taught individually, to replace or enhance a more traditional approach to the same or related content. Table 2 provides recommendations for inserting the lessons into a standard high school curriculum in biology.

How Does the Module Correlate with 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). Table 3 lists the content and teaching standards that this module primarily addresses.

How Does the BSCS 5E Instructional Model Promote Active, Collaborative, 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 specifically will provide a foundation on which we can build a detailed description of the instructional approach that the five lessons 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 associated with strategies that deserve to be labeled “active”:

- Students are involved in more than listening.
- Instructors 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 passive 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.

Table 2. Correlation between lessons and high school biology topics.

<table>
<thead>
<tr>
<th>High School Biology Topic</th>
<th>Lesson 1</th>
<th>Lesson 2</th>
<th>Lesson 3</th>
<th>Lesson 4</th>
<th>Lesson 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>evolution and natural selection</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>ethical issues related to genetic testing and screening</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>human genetic variation including genetic disorders</td>
<td>✔</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>multifactorial traits</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</tbody>
</table>
Table 3. Correlation to the National Science Education Standards.
A. The Content Standards

<table>
<thead>
<tr>
<th>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.</th>
<th>Correlation to Human Genetic Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Identify questions and concepts that guide scientific investigations.</td>
<td>Lessons 1, 2, and 3</td>
</tr>
<tr>
<td>• Use technology and mathematics to improve investigations and communications.</td>
<td>Lesson 2</td>
</tr>
<tr>
<td>• Formulate and revise scientific explanations and models using logic and evidence.</td>
<td>Lessons 2 and 3</td>
</tr>
<tr>
<td>• Recognize and analyze alternative explanations and models.</td>
<td>Lessons 2 and 3</td>
</tr>
<tr>
<td>• Communicate and defend a scientific argument.</td>
<td>Lesson 3</td>
</tr>
<tr>
<td>• Understanding scientific inquiry.</td>
<td>Lessons 2 and 3</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Standard C: As a result of their activities in grades 9–12, all students should develop understanding of the cell and the molecular basis of heridity.</th>
<th>Correlation to Human Genetic Variation</th>
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</thead>
<tbody>
<tr>
<td>• Cells store and use information to guide their functions.</td>
<td>Lessons 2, 3, and 5</td>
</tr>
<tr>
<td>• Cells can differentiate, and complex multicellular organisms are formed as a highly organized arrangement of differentiated cells.</td>
<td>Lessons 2 and 5</td>
</tr>
<tr>
<td>• In all organisms, the instructions for specifying the characteristics of the organism are carried in the DNA.</td>
<td>Lessons 2, 3, and 5</td>
</tr>
<tr>
<td>• Changes in DNA occur spontaneously at low rates.</td>
<td>Lessons 2, 3, and 5</td>
</tr>
<tr>
<td>• Species evolve over time.</td>
<td>Lesson 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>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.</th>
<th>Correlation to Human Genetic Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Scientists in different disciplines ask different questions, use different methods of investigation, and accept different types of evidence to support these explanations.</td>
<td>Lesson 3</td>
</tr>
<tr>
<td>• Science often advances with the introduction of new technologies.</td>
<td>Lesson 5</td>
</tr>
<tr>
<td>• Creativity, imagination, and a good knowledge base are all required in the work of science and engineering.</td>
<td>Lessons 1–5</td>
</tr>
<tr>
<td>• Science and technology are pursued for different purposes.</td>
<td>Lesson 5</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard F: As a result of activities in grades 9–12, all students should develop understanding of</th>
<th>Correlation to Human Genetic Variation</th>
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<tbody>
<tr>
<td>• personal and community health.</td>
<td>Lessons 2, 3, 4, and 5</td>
</tr>
<tr>
<td>• natural and human-induced hazards.</td>
<td>Lessons 2, 3, 4, and 5</td>
</tr>
<tr>
<td>• science and technology in local, national, and global challenges.</td>
<td>Lesson 5</td>
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<table>
<thead>
<tr>
<th>Standard G: As a result of activities in grades 9–12, all students should develop understanding of</th>
<th>Correlation to Human Genetic Variation</th>
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<tbody>
<tr>
<td>• science as a human endeavor.</td>
<td>Lesson 3</td>
</tr>
<tr>
<td>• nature of scientific knowledge.</td>
<td>Lessons 1–5</td>
</tr>
<tr>
<td>• historical perspectives.</td>
<td>Lesson 2</td>
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</table>
Table 3. Correlation to the National Science Education Standards.
B. The Teaching Standards

<table>
<thead>
<tr>
<th>Standard A: Teachers of science plan an inquiry-based science program for their students. In doing this, teachers</th>
<th>Correlation to Human Genetic Variation</th>
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<tbody>
<tr>
<td>• develop a framework of yearlong and short-term goals for students.</td>
<td>Each lesson provides short-term objectives for students. Tables 1, Conceptual Flow of the Lessons, and 6, Suggested Timeline for Teaching the Module, also help teachers plan. Using the modules helps teachers update their curriculum in response to their students’ interest in this topic. The focus on active, collaborative, and inquiry-based learning in the activities helps teachers meet this standard.</td>
</tr>
<tr>
<td>• select science content and adapt and design curriculum to meet the interests, knowledge, understanding, abilities, and experiences of students.</td>
<td></td>
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<tr>
<td>• select teaching and assessment strategies that support the development of student understanding and nurture a community of science learners.</td>
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<table>
<thead>
<tr>
<th>Standard B: Teachers of science guide and facilitate learning. In doing this, teachers</th>
<th>Correlation to Human Genetic Variation</th>
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<tbody>
<tr>
<td>• focus and support inquiries while interacting with students.</td>
<td>All of the activities in the module encourage and support student inquiry.</td>
</tr>
<tr>
<td>• orchestrate discourse among students about scientific ideas.</td>
<td>All of the activities in the module promote discourse among students.</td>
</tr>
<tr>
<td>• challenge students to accept and share responsibility for their own learning.</td>
<td>All of the activities in the module challenge students to accept and share responsibility for their learning. Combining the BSCS 5E Instructional Model with active, collaborative learning is an effective way of responding to the diversity of student backgrounds and learning styles. Annotations for the teacher throughout the activities provide many suggestions for how teachers can model these attributes.</td>
</tr>
<tr>
<td>• recognize and respond to student diversity and encourage all students to participate fully in science learning.</td>
<td></td>
</tr>
<tr>
<td>• encourage and model the skills of scientific inquiry, as well as the curiosity, openness to new ideas and data, and skepticism that characterize science.</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Standard C: Teachers of science engage in ongoing assessment of their teaching and of student learning. In doing this, teachers</th>
<th>Correlation to Human Genetic Variation</th>
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<tbody>
<tr>
<td>• use multiple methods and systematically gather data about student understanding and ability.</td>
<td>Each lesson has a variety of assessment components embedded within its structure. Annotations draw teachers’ attention to these opportunities for assessment.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.</td>
</tr>
<tr>
<td>• analyze assessment data to guide teaching.</td>
<td></td>
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</tbody>
</table>

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<tr>
<th>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</th>
<th>Correlation to Human Genetic Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• display and demand respect for the diverse ideas, skills, and experiences of all students.</td>
<td>The answers provided for teachers model these qualities.</td>
</tr>
<tr>
<td>• nurture collaboration among students.</td>
<td>All the activities are designed to be completed by students working in collaborative groups. All the discussions in the lessons model the rules of scientific discourse. The annotations for teachers provide many suggestions about how to model these skills, attitudes, and values.</td>
</tr>
<tr>
<td>• structure and facilitate ongoing formal and informal discussion based on a shared understanding of rules of scientific discourse.</td>
<td></td>
</tr>
<tr>
<td>• model and emphasize the skills, attitudes, and values of scientific inquiry.</td>
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</tbody>
</table>
The activities in this module were designed with the following assumptions about active learning (BSCS, 1999):

- 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.
- An activity promotes active learning to the degree that it offers extended opportunities for students to become personally engaged with the content.
- An activity promotes active learning to the degree that it involves students in thinking deeply about content.

The activities also make extensive use of collaborative 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 disciplines, 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 learning and cooperative learning, which have long theoretical and empirical histories, come out of different academic traditions, operate on different premises, and use 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 together.

Finally, the activities in the module use inquiry-based strategies. All truly inquiry-based activities share the characteristics of active learning. In addition, 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 biologists see the world, how they think about what they see, and how they draw conclusions that are consistent with observations and current knowledge. Such strategies say to the student, in effect, “This is science as a way of knowing.”

**The BSCS 5E Instructional Model**

The lessons in the module were designed using an instructional model to organize and sequence the experiences offered to students. This model, called the BSCS 5E Instructional 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 interactions 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 interprets 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 experience (Saunders, 1992). In the typical classroom, this means that fewer concepts and subjects can be covered 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 et al., 1995). In fact, the intensive thinking involved in constructing a thorough understanding of a few major ideas appears to benefit all students, regardless of ability.

Table 4 illustrates the key components of the BSCS 5E Instructional Model, so-called because it takes students through five phases of learning that are easily described using five words that begin with the letter “E”: Engage, Explore, Explain, Elaborate, and Evaluate.
### Table 4. The key components of the BSCS 5E Model: What the teacher does.

<table>
<thead>
<tr>
<th>Phase</th>
<th>What the teacher does that’s consistent with the 5E Model</th>
<th>What the teacher does that’s inconsistent with the 5E Model</th>
</tr>
</thead>
</table>
| Engage | • Creates interest  
• Generates curiosity  
• Raises questions  
• Elicits responses that uncover what students know or think about the concept or 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?” | • Tests vocabulary words, terms, and isolated facts  
• Introduces new ideas or concepts  
• Creates ambiguity  
• Promotes open-ended discussion unrelated to concept or skill |
### Table 5. The key components of the BSCS 5E Model: What the students do.

<table>
<thead>
<tr>
<th>Phase</th>
<th>What the students do that is consistent with the 5E Model</th>
<th>What the students do that is inconsistent with the 5E Model</th>
</tr>
</thead>
</table>
| Engage | • Become interested in and curious about the concept/topic  
• Express current understanding of a concept or idea  
• Raise questions such as, What do I already know about this? What do I want to know about this? How could I find out? | • Ask for the “right” answer  
• Offer the “right” answer  
• Insist on answers or explanations  
• Seek closure |
| Explore | • “Mess around” with materials and ideas  
• Conduct investigations in which they observe, describe, and record data  
• Try different ways to solve a problem or answer a question  
• Acquire a common set of experiences so they can compare results and ideas  
• Compare their ideas with those of others | • Let others do the thinking and exploring (passive involvement)  
• Work quietly with little or no interaction with others (only appropriate when exploring ideas or feelings)  
• Stop with one solution  
• Demand or seek closure |
| Explain | • Explain concepts and ideas in their own words  
• Base their explanations on evidence acquired during previous investigations  
• Become involved in student-to-student conversations in which they debate their ideas  
• Record their ideas and current understanding  
• Reflect on and perhaps revise their ideas  
• Express their ideas using appropriate scientific language  
• Compare their ideas with what scientists know and understand | • Propose explanations from “thin air” with no relationship to previous experiences  
• Bring up irrelevant experiences and examples  
• Accept explanations without justification  
• Ignore or dismiss other plausible explanations  
• Propose explanations without evidence to support their ideas |
| Elaborate | • Make conceptual connections between new and former experiences  
• Use what they have learned to explain a new object, event, organism, or idea  
• Use scientific terms and descriptions  
• Draw reasonable conclusions from evidence and data  
• Communicate their understanding to others | • Ignore previous information or evidence  
• Draw conclusions from “thin air”  
• Use terminology inappropriately and without understanding |
| Evaluate | • Demonstrate what they understand about the concept(s) and how well they can implement a skill  
• Compare their current thinking with that of others and perhaps revise their ideas  
• Assess their own progress by comparing their current understanding with their prior knowledge  
• Ask new questions that take them deeper into a concept or topic area | • Disregard evidence or previously accepted explanations in drawing conclusions  
• Offer only yes-or-no answers or memorized definitions or explanations as answers  
• Fail to express satisfactory explanations in their own words  
• Introduce new, irrelevant topics |
This instructional model allows students to share common experiences related to human genetic variation, to use and build on prior knowledge, to construct meaning, and to assess continually their understanding of a major concept. It avoids excessive use of lecture because research shows that 10 minutes is near the upper limit of comfortable attention that students give to lecture material, 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 describe how the 5Es are implemented across the lessons in this module. They also provide suggestions about effective teaching behaviors that help students experience each phase of the learning cycle.

**Engage**

Lesson 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 lesson 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 begin to think about how it relates to their previous experiences. Successful engagement results in students who are intrigued by the concepts they are about to study in depth.

**Explore**

Lesson 2, *The Meaning of Genetic Variation*, serves in a broad sense as the Explore phase of the model. In this lesson, students ask and answer questions about the ways human variation might be significant and then use resources on the curriculum’s Web site or in the print materials provided to explore the significance of genetic variation as the basis for evolution by natural selection.

**Explain**

*Molecular Medicine Comes of Age*, Lesson 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 are still student-centered. In Lesson 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.

**Elaborate**

During the Elaborate phase of the model, exemplified in this module by Lesson 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.

**Evaluate**

Finally, Lesson 5, *Making Decisions in the Face of Uncertainty*, acts as the Evaluate lesson 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 is also important that they receive some feedback on the adequacy of their explanations and understandings.
Evaluate lessons are complex and challenging, and Lesson 5 will stretch your students’ abilities to listen, think, and speak.

**What’s the Evidence for the Effectiveness of the BSCS 5E Instructional Model?**

Support from educational research studies for teaching science as inquiry is growing (for example, Geier et al., 2008; Hickey et al., 1999; Lynch et al., 2005; and Minner et al., 2009). A 2007 study, published in the *Journal of Research in Science Teaching* (Wilson et al., 2010), is particularly relevant to the *Human Genetic Variation* supplement.

In 2007, with funding from NIH, BSCS conducted a randomized, controlled trial to assess the effectiveness of the BSCS 5Es. The study used an adaptation of the NIH supplement *Sleep, Sleep Disorders, and Biological Rhythms*, developed by BSCS in 2003. Sixty high school students and one teacher participated. The students were randomly assigned to the experimental or the control group. In the experimental group, the teacher used a version of the sleep supplement that was very closely aligned with the theoretical underpinnings of the BSCS 5Es. For the control group, the teacher used a set of lessons based on the science content of the sleep supplement but aligned with the most commonplace instructional strategies found in U.S. science classrooms (as documented by Horizon Research; Weiss et al., 2003). Both groups had the same master teacher.

Students taught with the BSCS 5Es and an inquiry-based approach demonstrated significantly higher achievement for a range of important learning goals, especially when the results were adjusted for variance in pretest scores. The results were also consistent across time (both immediately after instruction and four weeks later). Improvements in student learning were particularly strong for measures of student reasoning and argumentation. The following chart (Table 6) highlights some of the study’s key findings. The results of the experiment strongly support the effectiveness of teaching with the BSCS 5Es.

Table 6. Differences in Performance of Students Receiving Inquiry-Based and Commonplace Instructional Approaches

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean for Students Receiving Commonplace Teaching</th>
<th>Mean for Students Receiving Inquiry-Based Teaching</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total test score pretest (out of 74)</td>
<td>31.11</td>
<td>29.23</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Total test score posttest</td>
<td>42.87</td>
<td>47.12</td>
<td>0.47</td>
</tr>
<tr>
<td>Reasoning pretest (fraction of responses at the highest level)</td>
<td>0.04</td>
<td>0.03</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Reasoning posttest</td>
<td>0.14</td>
<td>0.27</td>
<td>0.68</td>
</tr>
<tr>
<td>Score for articulating a claim (out of 3)</td>
<td>1.58</td>
<td>1.84</td>
<td>0.58</td>
</tr>
<tr>
<td>Score for using evidence in an explanation (out of 3)</td>
<td>1.67</td>
<td>2.01</td>
<td>0.74</td>
</tr>
<tr>
<td>Score for using reasoning in an explanation (out of 3)</td>
<td>1.57</td>
<td>1.89</td>
<td>0.59</td>
</tr>
</tbody>
</table>


*Note: Effect size is a convenient way of quantifying the amount of difference between two treatments. This study used the standardized mean difference (the difference in the means divided by the standard deviation, also known as Cohen’s d). The posttest scores controlled for the variance in students’ pretest scores. The reasoning posttest scores controlled for variance in students’ reasoning pretest scores at the highest level.*
Evidence also suggests that the BSCS 5Es are effective in changing students’ attitudes on important issues. In a research study conducted during the field test for the NIH curriculum supplement *The Science of Mental Illness*, BSCS partnered with researchers at the University of Chicago and the National Institute of Mental Health. The study investigated whether a short-term educational experience would change students’ attitudes about mental illness. The results showed that after completing the curriculum supplement, students stigmatized mental illness less than they had beforehand. The decrease in stigmatizing attitudes was statistically significant (Corrigan et al., 2007; Watson et al., 2004).

**How Does the Module Support Ongoing Assessment?**

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 learning 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 lessons. These embedded assessment opportunities include one or more of the following strategies:

- performance-based activities (for example, structured discussions of potentially controversial issues);
- oral presentations to the class (for example, role playing); 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, problem-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 a description of what you can assess appear in the margin beside each embedded assessment.

**How Can Controversial Topics Be Handled in the Classroom?**

Teachers sometimes feel that the discussion of values is inappropriate in the science classroom or that it detracts from the learning of “real” science. The lessons in this module, however, are based on 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.

In this module, students have a variety of opportunities 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 will also depend on how you handle your role as facilitator. Your language and attitude factor into the flow of ideas and the quality of exchange among the students.

The following guidelines may help you think about how to guide your students in discussions that balance factual information with values.

- **Remain neutral.** Neutrality may be the single most important characteristic of a successful discussion facilitator.
• Encourage 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 that are a matter of values. Maintaining this distinction is particularly important as students discuss the issues about genetic testing raised in Lesson 5. Students should understand the importance of accurate information to any discussion and should recognize the importance of distinguishing factual information from opinions.

• Keep the discussion relevant and moving forward by questioning or posing appropriate problems or hypothetical situations. Encourage everyone to contribute, but do not force reluctant students into the discussion.

• Emphasize that everyone must be open to hearing and considering diverse views.

• Use unbiased questioning to help students critically examine all views presented.

• Allow for the discussion of all feelings and opinions.

• Avoid seeking consensus on all issues. This is particularly important in Lesson 5. The multifaceted issues that the students discuss result in the presentation of divergent views, and students should learn that this is acceptable.

• Keep your own views out 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.”

• Acknowledge all contributions in the same evenhanded manner. If the class senses that you favor one idea over another, you will inhibit open debate and discussion. For example, avoid praising the substance or content of comments. Instead, acknowledge the willingness of students to contribute by making comments such as, “Thanks for that idea” or “Thanks for those comments.” As you display an open attitude, a similarly accepting climate will begin to develop within the class.

• Create 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.

• Insist on a nonhostile environment in the classroom. Help your students learn to respond to ideas instead of to the individuals presenting those ideas.

• Respect silence. Reflective discussions are often slow. If you break the silence, your students may allow you to dominate the discussion.

• Finally, at the end of the discussion, ask your students to summarize the points they and their classmates have made. Let students know that your respect for them does not depend on their opinion about any controversial issue.

Implementing the Module
Using the Student Lessons

The heart of this module is the set of five lessons, which we hope will carry important concepts related to disease and public health to your students. To review the concepts in detail, refer to Table 1 in “Implementing the Module” (page 3).

**Format of the Lessons**
As you scan the lessons, you will find that each contains several major features.

- **At a Glance** gives you a convenient summary of the lesson.
  - The **Overview** provides a short summary of what students do.
  - **Major Concepts** states the central idea(s) the lesson is designed to convey.
  - **Objectives** list three to five specific understandings or abilities students should have after completing the lesson.
  - **Prerequisite Knowledge** alerts you to the understandings and skills students should have before beginning the lesson.
  - **The Basic Science–Health Connection** describes how the lesson illustrates the relationship between basic science and personal and public health. The mission of 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. 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 lesson in a context and provides a short overview of its key components.

- **In Advance** provides instructions for collecting the materials, photocopying, and other preparations needed for the activities in the lesson.

- **Procedure** outlines the lesson’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,
  - assessing student understanding, and
  - focusing students’ attention on the lesson’s major concepts during its closing steps.

Other icons indicate

- when to use the Web site (see “Using the Web Site” for instructions; a print-based alternative is provided for classes that don’t have access to the Internet) and

- the beginning of a print-based alternative version.

- **Potential Extensions** describes ways you can extend or enrich the lesson.
Figure 2. A Möbius strip is a one-sided, one-edged loop. Test this by making a paper 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 Möbius strip as a metaphor for the relationship between basic science and personal and public health.

The Lesson Organizer at the end of each lesson provides a quick view of the steps of each activity, including icons that notify you when you will need to make masters and transparencies and when there’s an online component.

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

Lessons 2 and 5 (The Meaning of Genetic Variation and Making Decisions in the Face of Uncertainty) use materials on the Human Genetic Variation Web site. Lesson 3 (Molecular Medicine Comes of Age) includes a Web-based option for teachers who wish to use it. For information about the site, see “Using the Web Site” on page 17. If you do not have enough computers with Internet access, you can use the print-based alternatives.

Timeline for Teaching the Module
The suggested timeline (Table 7) outlines a plan for completing the five lessons. The plan assumes that your class periods are 45 to 50 minutes and that you will teach the lessons on consecutive days. It’s important to review the timeline before teaching the module. Instructions for setting up computers are under “Using the Web Site” (page 17) and online at http://science.education.nih.gov/supplements/genetic/teacher and for preparing other materials, under In Advance in each lesson.

Table 7. Suggested timeline for teaching the module.*

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 weeks ahead</td>
<td>(Optional) Reserve computers and bookmark the Web site. Collect supplies.</td>
</tr>
<tr>
<td>1 week ahead</td>
<td>Copy masters. Make transparencies.</td>
</tr>
<tr>
<td>Day 1</td>
<td>Lesson 1</td>
</tr>
<tr>
<td>Day 2</td>
<td>Lesson 2 (Day 1)</td>
</tr>
<tr>
<td>Day 3</td>
<td>Lesson 2 (Day 2)</td>
</tr>
<tr>
<td>Day 4</td>
<td>Lesson 3</td>
</tr>
<tr>
<td>Day 5</td>
<td>Lesson 4</td>
</tr>
<tr>
<td>Day 6</td>
<td>Lesson 5</td>
</tr>
</tbody>
</table>

* Assuming class periods of 45 to 50 minutes.
Using the Web Site

The Web component of Human Genetic Variation is a wonderful tool that you can use to help organize your use of the module, engage student interest in learning, and help orchestrate and individualize instruction. The site features simulations, illustrations, and videos that articulate with the lessons. To access the curriculum's home page, go to http://science.education.nih.gov/supplements/genetic. (If your classes don't have access to the Internet, you can use the print alternatives included with the lessons.)

The Web site includes the following resources:

• information about the National Institutes of Health and National Human Genome Research Institute;
• printable files of this module;
• printable files of the print-based alternatives for Lessons 2 and 5;
• a video documentary and a reference database for Lesson 2;
• optional video clips in support of Lesson 3; and
• the video clips and reference database for Lesson 5.

Collaborative Groups

We designed all the activities in this module to be completed by groups of students working together. Although individual students working alone can complete many of the steps, this strategy will not stimulate the types of student-student interactions that are part of active, collaborative, inquiry-based learning. Therefore, we recommend that you organize collaborative groups of between two and four students each, depending on the number of computers available. If necessary, up to six students may work as a group, although the students may not be as involved in the activity. Students in groups larger than this are likely to have difficulty organizing the student-computer interactions equitably. This can lead to one or two students’ assuming the primary responsibility for the computer-based work. Although large groups can be efficient, they do not allow all students to experience the in-depth discovery and analysis that the Web site was designed to stimulate. Group members not involved directly may become bored or disinterested.

If you are teaching all five lessons as a unit, we recommend that you keep your students in the same collaborative groups for all the activities. This will allow each group to develop a shared experience with the Web site and with the ideas and issues the activities present. A shared experience will also enhance your students’ perceptions of the lessons 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 variation.

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 lessons. For example, if you have only one computer available, you may want students to complete the Web-based work over an extended time period. You can do this several ways. The most practical one is to use your computer as a center along with several other centers at which students complete other activities. In this approach, students rotate through the computer center, eventually completing the Web-based work you have assigned.

A second way to structure the lessons if you only have one computer available is to use a projection system to display the computer monitor onto a screen for the whole class to see. Giving selected students in the class the opportunity to manipulate the Web activities in response to suggestions and requests from the class can give students some of the same autonomy in their learning they would have gained from working in small groups.

Web Activities for People with Disabilities
The Office of Science Education provides access to the Curriculum Supplement Series for people with disabilities. The online versions of this series comply with Section 508 of the Rehabilitation Act. If you use assistive technology (such as a Braille or screen reader) and have trouble accessing any materials on our Web site, please let us know. We’ll need a description of the problem, the format in which you would like to receive the material, the Web address of the requested material, and your contact information.

Contact us at
Curriculum Supplement Series
Office of Science Education
National Institutes of Health
6100 Executive Boulevard, Suite 3E01
Bethesda, MD 20892-7520
or
supplements@science.education.nih.gov
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 to understand ourselves better. 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 the perception that such study has enormous potential to improve human health. This perception and its realization in the discoveries of the past 30 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 led to strong support for 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, which 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) rapidly transformed the study of human genetics, ultimately allowing...

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**Figure 3.** Microarrays, sometimes called gene chips, provide snapshots of all the genes that are active in a cell at a particular time.
scientists to study the detailed structure and functions of individual human genes, and 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 draw on 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, transmission genetics, involved crossing organisms and studying the offspring's 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,
• identified the gametes as the vehicles that transmit genetic information from one generation to another, and
• 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 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 are also 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 these limitations made identifying and studying genes in humans both tedious and slow.

In the past 60 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 examples of 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 allowed workers to sequence the human genome at an unprecedented rate.

One relatively new technique, DNA microarray technology (also called DNA chip technology), is a revolutionary tool designed to identify mutations in genes or to survey expression of tens of thousands of genes in one experiment.
For an excellent review—with great illustrations—of how microarray technology is being used in medicine, see the article by Feero et al. (2010), listed in the References section.

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 one used to make computer microchips. On its surface, it contains synthetic single-stranded DNA sequences identical to those 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 from someone else 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 have a mutation, the mutant sequence on the chip will hybridize to the patient’s sample but not to the normal DNA, causing 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 microarray technology has the potential to significantly reduce the time and expense involved in genetic testing. This technology or others like it may 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 by the patterns of gene activity in the tumor cells and then be able to design treatment strategies for 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 $3 \times 10^9$ 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 0.1 percent. This means that about 1 base pair out of every 1,000 will be different between any two individuals. Any two (diploid) people have about $6 \times 10^6$ base pairs that are different, an important reason for the development of automated procedures for analyzing 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,
**Human Genetic Variation**

SNP occurs, 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.

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.

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 *mutL* and *mutS*. 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 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 apparent adaptive significance. Some variations (for example, a neutral mutation) alter the amino acid sequence of the resulting protein but produce no detectable change in its function. Other variations (for example, a silent mutation) do not even change the amino acid sequence. Furthermore, only a small percentage of the DNA sequences in the human genome is 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 detectable impact.

![Venn diagram showing variation within and between populations](image)

**Figure 4.** Most human genetic variation occurs within populations.
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 a 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 is associated with disease, of course, as classic single-gene disorders such as sickle cell disease, cystic fibrosis, and Duchenne muscular dystrophy remind us. Increasingly, research is also uncovering genetic variations associated with 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 disorder (often called 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 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 are generally 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 are generally of older origin and have a smaller, more gradual effect on homeostasis. Their onset is generally in adulthood. The last two characteristics make the ability to detect genetic variations that increase the 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 suggests, 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, which we have traditionally placed in a completely different category from 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 thus 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 has 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 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 healthcare 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 healthcare strategy. Newborn screening for diseases like phenylketonuria (PKU) has been going on for 40 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 views a particular disease and can also change the pattern of care that people in affected families 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 40 to 50 percent of all inherited breast cancer, or about 3 percent of all breast cancer. Variants of BRCA2, located on the long arm of chromosome 13, appear to account for about 20 to 30 percent of all inherited breast cancer.
Variants of these genes also slightly increase 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 one of hundreds of significant mutations already detected in the \textit{BRCA1} gene. For a woman with a family history of breast cancer, the knowledge that she carries one of the variants of \textit{BRCA1} or \textit{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 a 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 \textbf{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 \textit{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, physicians will use genetic tests to match drugs to an individual patient’s body chemistry so they can prescribe the safest and most effective drugs and dosages. After identifying the genotypes that determine individual responses to particular drugs, pharmaceutical companies will likely 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 is also 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 the disease 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 it may be present but not functioning properly. In some mutations, synthesis of CFTR protein is interrupted, and the cells produce no CFTR molecules at all.

Although all 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 levels 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 degraded prematurely, before they reach the cell membrane. This finding suggests that drug treatments that would enhance transport of the CFTR protein to the cell membrane or prevent its degradation could yield important benefits for patients with delta F508 CFTR. Such drug strategies have been vigorously pursued by the Cystic Fibrosis Foundation, leading to clinical trials of compounds that both assist protein processing and encourage proper functioning of CFTR once it reaches the membrane.

Finally, the identification, cloning, and sequencing of a disease-related gene can open the door to the development of strategies for treating the disease that use 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 successfully to treat inherited immune deficiencies. These diseases were chosen because the mutant gene causing the disease was known and there was evidence that even a few corrected cells could restore complete immune function. Since 2000, 37 children with either X-linked severe combined immune deficiency (X-SCID, the “Bubble Boy Disease”) or ADA-SCID (deficiency of the adenosine deaminase enzyme that prevents the correct development and functioning of T-lymphocytes) have been treated with this approach. Bone marrow cells from these patients were exposed to a virus containing a normal copy of the mutant gene and were then transplanted back into the patients. To date, 33 of these 37 patients (89 percent) have been cured. Two patients had very low rates of gene transfer, one patient failed the bone marrow transplant, and one patient died of an adverse event related to the gene therapy. In comparison, the best conventional therapy for SCID is bone marrow transplantation from a compatible donor. If compatible bone marrow donors had been available for these patients, only 65 percent would be expected to survive, so gene therapy is the treatment of choice for these diseases.

Cancer presents a complicated problem for any treatment because the exact mutation causing the disease is not usually known and therapies can injure the healthy cells surrounding the tumor. Gene therapy is being used to treat a variety of cancers, however. One successful strategy is to use gene therapy to modify the body’s white blood cells so that they become efficient killers of tumor cells. In one study,
patients with malignant lymphomas that had been resistant to all other therapies were treated with gene-modified white blood cells. More than three-quarters of the patients responded to the treatment, and 41 percent were completely cured of the disease. In another study, genetic modifications were able to direct white blood cells to another type of cancer: neuroblastoma, a common childhood cancer with no effective treatment. The neuroblastoma tumors shrank or disappeared in half the patients. Because of the specificity of these anticancer cells, there were no significant side effects. All told, more than 1,000 patients have participated in cancer gene therapy studies, and none of them has died as a consequence of the gene therapy. Because of the success of these studies, gene therapy is now being used earlier in the treatment of cancer, when the prospects for a cure are better.

Gene therapy is being developed for many other diseases as well. Dogs have been cured of all these diseases by gene therapy:
- hemophilia,
- several enzyme deficiencies that slowly kill brain and muscle cells because they store toxic substances,
- a third immune-deficiency disease, and
- hereditary blindness.

The success of these animal studies has allowed the therapies to be developed for humans with the same diseases. A recent study of gene therapy for hereditary blindness has shown vast improvement in the vision of the treated patients, and it is hoped that this result will lead to effective gene therapy for other sight disorders such as glaucoma.

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 healthcare strategies based on knowledge of a gene's structure and function. The new knowledge and technologies that emerged from HGP-related research have also reduced 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, now that the HGP is completed, finding a gene associated with a Mendelian disorder can be accomplished in just weeks at a cost of less than $10,000.

Over the past few years, research into human genetic variation has made the dramatic transition from focusing primarily on genes associated with single-gene disorders, which are relatively rare in the human population, to focusing on genes associated with common 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 will also lead to increased testing and the development of new interventions that will likely 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 would also raise a number of complex ethical, legal, and social issues. To anticipate and address these issues, they established in 1990 the Ethical, Legal, and Social Implications (ELSI) program. 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.
Human Genetic Variation

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 past 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 and multifaceted, and they 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 a 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 aspects of any ethics discussion is the variety of ways 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 can also 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. Knowledge of science is also 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 diverse 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, there is no treatment for it. There is not necessarily an 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. On the other hand, 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. Lesson 5, Making Decisions in the Face
of Uncertainty, presents students with the 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 Lesson 5 is prudential decision making, which involves the ability to avoid unnecessary risk when it is uncertain whether an event will actually occur. By completing the lesson, 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 and ethics both 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. 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 publicly accessible scientific and medical knowledge. As a consequence, we can think about the relationships among knowledge, choice, behavior, and human health in the following ways:

**Knowledge (what is known and not known)**

+ **Choice** = **Power**

**Power + Behavior = Enhanced Human Health**

*(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.
References


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Additional Resources for Teachers

Online Genetics Education Resources

**Access Excellence**
http://www.accessexcellence.org
A series of learning modules on multiple science and health topics, including biotech and genetics. Sponsored by the National Health Museum, a nonprofit organization founded by former U.S. Surgeon General C. Everett Koop.

**American Medical Association: Family History Tools**
http://www.ama-assn.org/ama/pub/category/2380.html
Tools for gathering family history.

**The DNA Files**
http://www.dnafiles.org/
A series of 14 one-hour public radio documentaries and related information.

**Dolan DNA Learning Center**
http://www.dnalc.org/
Dolan’s mission is to prepare students and families to thrive in the gene age, envisioning a day when all elementary students are exposed to principles of genetics and disease risk; when all high school students have the opportunity to do hands-on experiments with DNA; and when all families have access to genetic information they need to make informed healthcare choices. Includes an interactive DNA timeline.

**Foundations of Classical Genetics**
http://www.esp.org/foundations/genetics/classical
Complete versions of classic genetics works written between 350 A.D. and 1932.

**GeneTests**
http://www.genetests.org/
Information for health professionals about hundreds of genetic tests.

**Genetic Science Learning Center**
http://learn.genetics.utah.edu/
From the Eccles Institute of Human Genetics at the University of Utah, a Web site created to help people understand how genetics affects their lives and society.

**Genetics and Molecular Medicine (American Medical Association)**
http://www.ama-assn.org/ama/pub/category/1799.html
Links to current articles and other resources.

**Genetics Education Center**
http://www.kumc.edu/gec
A comprehensive listing of genetics education resources, including networking sites, documentary films, lectures, booklets, activities, and programs. Compiled by the Genetics Education Center, University of Kansas Medical Center.

**Genetics Home Reference**
Provides consumer information about genetic conditions and the genes or chromosomes responsible for those conditions.

**Genetics Origins**
http://www.geneticorigins.org/
Provides biochemical methods and computer tools to allow students to use their own DNA “fingerprints” as a starting point in the study of human evolution.
**Human Genetic Variation**

**The Genomic Resource Centre**
http://www.who.int/genomics/en
From the World Health Organization, provides information and raises awareness on human genomics.

**Human Genome Epidemiology Network (HuGENet)**
http://www.cdc.gov/genomics/hugenet/default.htm
Hosted by the Centers for Disease Control and Prevention (CDC), an international collaboration for sharing population-based human genome epidemiologic information.

**Human Genome Project Education Resources**
http://www.ornl.gov/hgmis/education/education.html
An extensive collection of publications, teaching aids, and additional internet resources. Hosted by the Human Genome Program of the U.S. Department of Energy.

**Human Genome Resources**
Comprehensive one-stop genomic information center. Hosted by the National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM).

**MendelWeb**
http://www.mendelweb.org/
Gregor Mendel's papers in English and German and related materials.

**National Coalition for Health Professional Education in Genetics**
http://www.nchpeg.org/
Core competencies in genetics and reviews of education programs.

**National Library of Medicine: PubMed**
Basic search engine for biomedical research, including research and commentary about clinical research ethics and regulations.

**The New Genetics: A Resource for Students and Teachers**
http://www4.umdnj.edu/camlbweb/teachgen.html
Links to genetic education resources.

**Omics Gateway**
http://www.nature.com/genomics

**Public Health Genomics**
http://www.cdc.gov/genomics/
Resources on genetics, including journals, reports, and fact sheets. Also includes online multimedia presentations ranging from basic genetics to latest research.

**Understanding Gene Testing**
http://www.cancer.gov/cancertopics/understandingcancer/genetesting
An informative, illustrated tutorial on genes and genetic testing. Hosted by the National Cancer Institute.

**Your Genome**
http://www.yourgenome.org
Produced by the Wellcome Trust Sanger Institute, Your Genome provides an introduction to the main concepts of DNA, genes, and genomes, focusing on basic questions such as, What is a genome? and What are genes? There is also an introduction to the Human Genome Project and much more. Produced by the Wellcome Trust Sanger Institute.

**ELSI Policy and Legislation Online**

**Bioethics Resources on the Web**
http://bioethics.od.nih.gov/
NIH links to bioethics resources.

**bioethics.net**
http://www.bioethics.net/
The American Journal of Bioethics—news, articles, and commentary.
DNA Patent Database
http://dnapatents.georgetown.edu

The Council for Responsible Genetics
http://www.gene-watch.org
Information on the social, ethical, and environmental implications of genetic technologies.

Genethics.ca
http://www.genethics.ca/
Information on the social, ethical, and policy issues associated with genetic and genomic knowledge and technology.

Genetics and Public Policy Center
http://www.dnpolicy.org
Information on genetic technologies and genetic policies for the public, media, and policymakers.

HumGen International
http://www.humgen.org/int/index_lang.cfm?lang=1
Access to a comprehensive international database on the legal, social, and ethical aspects of human genetics.

National Information Resources on Ethics and Human Genetics
http://bioethics.georgetown.edu/nirehg/
Links to resources on ethics and human genetics.

National Human Genome Research Institute ELSI Research Program
http://www.genome.gov/
Information, articles, and links on a wide range of ethical, legal, and social issues from NHGRI.

The President’s Council on Bioethics
http://www.bioethics.gov
Information on current bioethical issues.

Family Medical History and Tools Resources Online

My Family Health Portrait (Web Version Only)
https://familyhistory.hhs.gov/fhh-web/home.action
The Web-based tool from the U.S. Surgeon General’s Family History Initiative for use on any computer with an Internet connection and a Web browser.

My Family Health Portrait (downloadable tool and Web version)
http://www.hhs.gov/familyhistory/portrait/index.html
The original 2004 tool from the U.S. Surgeon General’s Family History Initiative to download and use on your computer.

National Society for Genetic Counselors: Family History Tool
http://www.nsgc.org/About/FamilyHistoryTool/tabid/226/Default.aspx
Information on collecting family health history.

Genetic Counseling, Support, and Advocacy Groups Online

Coalition for Genetic Fairness
http://www.geneticfairness.org/index.html
Advocacy group for federal legislation regarding genetics discrimination through the National Partnership for Women and Families.

Find a Genetic Counselor
http://www.nsgc.org/FindaGeneticCounselor/tabid/64/Default.aspx
A searchable database of genetics counseling services. Search by location, name, institution, type of practice, or specialty. Hosted by the National Society of Genetic Counselors.

GeneTests: Clinic Directory
Database of genetics clinics, searchable by location, population served, and specialty.
Human Genetic Variation

The Genetic Alliance
http://www.geneticalliance.org
Wide array of genetic-related information.

Genetics and Rare Conditions Site
http://www.kumc.edu/gec/support
Information on genetic conditions and birth defects for professionals, educators, and individuals, including national and international advocacy and support groups. Comprehensive list of resources organized by disease and condition. Hosted by the University of Kansas Medical Center.

Mountain States Genetic Network (MoST GeNe)
http://www.mostgene.org/topics/cclin01.htm
Information on genetic counseling.

National Organization for Rare Disorders
http://www.rarediseases.org
Wide array of genetic-related information.

General Health Information Resources Online

MedlinePlus
http://www.nlm.nih.gov/medlineplus/
The National Institutes of Health’s Web site for patients and their families and friends. Offers reliable, up-to-date information about diseases, conditions, and wellness issues in easily understood language.

National Institutes of Health (NIH) Health Information Resources
http://www.health.nih.gov/
A comprehensive guide to health information, including National Institutes of Health (NIH) programs and resources, as well as information on clinical trials, drugs, and health conditions.

Public Health Genomics
http://www.cdc.gov/genomics/default.htm
Resources on genetics including journals, reports, and fact sheets. Also includes online multimedia presentations ranging from basic genetics to the latest research. Hosted by the Centers for Disease Control and Prevention (CDC).

Genetic, Rare, and Orphan Disease Resources Online

Genetics and Rare Conditions Site
http://www.kumc.edu/gec/support
Alphabetical index of genetic disorders with links to disease-related associations, support groups, foundations, online discussion groups, and listservs. Hosted by the University of Kansas Medical Center.

Genetics Home Reference
Consumer information about genetic conditions and the genes responsible for those conditions. Hosted by the National Library of Medicine (NLM).

Genome Research Resources Online

Cancer Genome Anatomy Project
http://cgap.nci.nih.gov
Access to all CGAP data and biological resources.

Ensembl
http://www.ensembl.org
Access to DNA and protein sequences with automatic baseline annotation.

International HapMap Project
http://snp.cshl.org
A variety of ways to query for single nucleotide polymorphisms (SNPs) in the human genome.

National Center for Biotechnology Information—Genome Resources Guide
Views of chromosomes, maps, and loci; links to other NCBI resources.

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Information about human genes and disease.

University of California–Santa Cruz (UCSC) Genome Bioinformatics
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Screening, Testing, and Risk Assessment Resources Online

National Birth Defects Prevention Network
http://www nbdpn.org
Network of birth-defect care providers.

National Cancer Institute: Breast Cancer Risk Assessment Tool
http://bcra.nci.nih.gov/brc/
Interactive tool to measure a woman’s risk of invasive breast cancer.

National Newborn Screening and Genetics Resource Center
http://genes-r-us.uthscsa.edu/
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Understanding Cancer Series: Gene Testing
http://www.cancer.gov/cancertopics/understandingcancer/genetesting/
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Glossary


ACGT: ACGT is an acronym for the four types of bases found in a DNA molecule: adenine (A), cytosine (C), guanine (G), and thymine (T). A DNA molecule consists of two strands wound around each other, with each strand held together by bonds between the bases. Adenine pairs with thymine, and cytosine pairs with guanine. The sequence of bases in a portion of a DNA molecule, called a gene, carries the instructions needed to assemble a protein.

acquired immunodeficiency syndrome (AIDS): AIDS is a collection of symptoms known as acquired immunodeficiency syndrome. It is caused by infection with the human immunodeficiency virus (HIV), which leads to loss of immune cells and leaves individuals susceptible to other infections and the development of certain types of cancers. There is no cure for AIDS, though drugs can slow down and stabilize the disease's progress.

adenine: Adenine (A) is one of four chemical bases in DNA; the other three are cytosine (C), guanine (G), and thymine (T). Within the DNA molecule, adenine bases located on one strand form chemical bonds with thymine bases on the opposite strand. The sequence of four DNA bases encodes the cell's genetic instructions. A form of adenine called adenosine triphosphate (ATP) serves as an energy storage molecule and is used to power many chemical reactions within the cell.

allele: An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. Though the term “allele” was originally used to describe variation among genes, it now also refers to variation among noncoding DNA sequences.

amino acids: Amino acids are a set of 20 different molecules used to build proteins. Proteins consist of one or more chains of amino acids called polypeptides. The sequence of the amino acid chain causes the polypeptide to fold into a biologically active shape. The amino acid sequences of proteins are encoded in the genes.

ancestry-informative markers: Ancestry-informative markers are sets of polymorphisms for a particular DNA sequence that appear in substantially different frequencies between populations from different geographical regions of the world. Ancestry-informative markers can be used to estimate the geographical origins of the ancestors of an individual typically by continent of origin (Africa, Asia, or Europe).

animal model: An animal model is a nonhuman species used in medical research because it can mimic aspects of a disease found in humans. Animal models are used to obtain information about a disease and its prevention, diagnosis, and treatment. By using animals, researchers can carry out experiments that would be impractical or ethically prohibited with humans.

antibody: An antibody is a protein component of the immune system that circulates in the blood and recognizes and neutralizes foreign substances such as bacteria and viruses. After exposure to a foreign substance, called an antigen, antibodies continue to circulate in the blood, providing protection against future exposures to that antigen.
**anticodon:** An anticodon is a trinucleotide sequence complementary to that of a corresponding codon in a messenger RNA (mRNA) sequence. An anticodon is found at one end of a transfer RNA (tRNA) molecule. During protein synthesis, each time an amino acid is added to the growing protein, a tRNA forms base pairs with its complementary sequence on the mRNA molecule, ensuring that the appropriate amino acid is inserted into the protein.

**antisense:** Antisense is the noncoding DNA strand of a gene. A cell uses antisense DNA as a template for producing messenger RNA (mRNA), which directs the synthesis of a protein. Antisense can also refer to a method for silencing genes. To silence a target gene, a second gene is introduced that produces an mRNA complementary to that produced from the target gene. These two mRNAs can interact to form a double-stranded structure that cannot be used to direct protein synthesis.

**apoptosis:** Apoptosis is the process of programmed cell death. It is used during early development to eliminate unwanted cells—for example, those between the fingers of a developing hand. In adults, apoptosis is used to rid the body of cells that have been damaged beyond repair. Apoptosis also plays a role in preventing cancer. If apoptosis is for some reason prevented, it can lead to uncontrolled cell division and the subsequent development of a tumor.

**autism:** Autism is a developmental brain disorder characterized by impaired social interactions, communication problems, and repetitive behaviors. Symptoms usually appear before the age of three. The exact cause of autism is not known; however, it is likely influenced by genetics. Autism is one of a group of related developmental disorders called autism spectrum disorders (ASDs). Other ASDs include Asperger syndrome and Rett syndrome.

**autosomal dominant:** Autosomal dominance is a pattern of inheritance characteristic of some genetic diseases. “Autosomal” means that the gene in question is located on one of the numbered, or non sex, chromosomes. “Dominant” means that a single copy of the disease-associated mutation is enough to cause the disease. This is in contrast to a recessive disorder, where two copies of the mutation are needed to cause the disease. Huntington’s disease is a common example of an autosomal dominant genetic disorder.

**autosome:** An autosome is any of the numbered chromosomes, as opposed to the sex chromosomes. Humans have 22 pairs of autosomes and one pair of sex chromosomes (the X and Y). Autosomes are numbered roughly in relation to their sizes. That is, chromosome 1 has about 2,800 genes, while chromosome 22 has about 750 genes.

**bacteria:** Bacteria are small single-celled organisms. Bacteria are found almost everywhere on Earth and are vital to the planet’s ecosystems. Some species can live under extreme conditions of temperature and pressure. The human body is full of bacteria; in fact, it contains more bacterial cells than human cells. Most bacteria in the body are harmless, and some are even helpful. A relatively small number of species cause disease.

**bacterial artificial chromosome (BAC):** A bacterial artificial chromosome (BAC) is an engineered DNA molecule used to clone DNA sequences in bacterial cells (for example, Escherichia coli). BACs are often used in connection with DNA sequencing. Segments of an organism’s DNA, ranging from 100,000 to about 300,000 base pairs, can be inserted into BACs. The BACs, with their inserted DNA, are then taken up by bacterial cells. As the bacterial cells grow and divide, they amplify the BAC DNA, which can then be isolated and used in sequencing DNA.
**base pair:** A base pair is two chemical bases bonded to one another forming a “rung of the DNA ladder.” The DNA molecule consists of two strands that wind around each other like a twisted ladder. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases—adenine (A), cytosine (C), guanine (G), or thymine (T). The two strands are held together by hydrogen bonds between the bases, with adenine forming a base pair with thymine, and cytosine forming a base pair with guanine.

**bioinformatics:** Bioinformatics is a subdiscipline of biology and computer science concerned with the acquisition, storage, analysis, and dissemination of biological data, most often DNA and amino acid sequences. Bioinformatics uses computer programs for a variety of applications, including determining gene and protein functions, establishing evolutionary relationships, and predicting the three-dimensional shapes of proteins.

**birth defect:** A birth defect is an abnormality present at birth. Also called a congenital defect, it can be caused by a genetic mutation, an unfavorable environment during pregnancy, or a combination of both. The effect of a birth defect can be mild, severe, or incompatible with life.

**BRCA1/BRCA2:** BRCA1 and BRCA2 are the first two genes found to be associated with inherited forms of breast cancer. Both genes normally act as tumor suppressors, meaning that they help regulate cell division. When these genes are rendered inactive due to mutation, uncontrolled cell growth results, leading to breast cancer. Women with mutations in either gene have a much higher risk of developing breast cancer than women without mutations in the genes.

**cancer:** Cancer is a group of diseases characterized by uncontrolled cell growth. Cancer begins when a single cell mutates, resulting in a breakdown of the normal regulatory controls that keep cell division in check. These mutations can be inherited, caused by errors in DNA replication, or result from exposure to harmful chemicals. A cancerous tumor can spread to other parts of the body and, if left untreated, be fatal.

**candidate gene:** A candidate gene is a gene whose chromosomal location is associated with a particular disease or other phenotype. Because of its location, the gene is suspected of causing the disease or other phenotype.

**carcinogen:** A carcinogen is an agent with the capacity to cause cancer in humans. Carcinogens may be natural, such as aflatoxin, which is produced by a fungus and sometimes found on stored grains, or manmade, such as asbestos or tobacco smoke. Carcinogens work by interacting with a cell’s DNA and inducing genetic mutations.

**carrier:** A carrier is an individual who carries and is capable of passing on a genetic mutation associated with a disease and may or may not display disease symptoms. Carriers are associated with diseases inherited as recessive traits. In order to have the disease, an individual must have inherited mutated alleles from both parents. An individual having one normal allele and one mutated allele does not have the disease. Two carriers may produce children with the disease.

**carrier screening:** Carrier screening is a type of genetic testing performed on people who display no symptoms for a genetic disorder but may be at risk for passing it on to their children. A carrier for a genetic disorder has inherited one normal and one abnormal allele for a gene associated with the disorder. A child must inherit two abnormal alleles for symptoms to appear. Prospective parents with a family history of a genetic disorder are candidates for carrier screening.

**cell:** A cell is the basic building block of living things. All cells can be sorted into one of two groups: eukaryotes and prokaryotes. A eukaryote has a nucleus and membrane-bound organelles, while a prokaryote does not. Plants and animals are made of numerous eukaryotic cells, while many microbes, such as bacteria, consist of single cells. An adult human body is estimated to contain between 10 and 100 trillion cells.
cell cycle: A cell cycle is a series of events that takes place in a cell as it grows and divides. A cell spends most of its time in what is called interphase, and during this time, it grows, replicates its chromosomes, and prepares for cell division. The cell then leaves interphase, undergoes mitosis, and completes its division. The resulting cells, known as daughter cells, each enter their own interphase and begin a new round of the cell cycle.

cell membrane (plasma membrane): The cell membrane, also called the plasma membrane, is found in all cells and separates the interior of the cell from the outside environment. The cell membrane consists of a lipid bilayer that is semipermeable. The cell membrane regulates the transport of materials entering and exiting the cell.

centimorgan: A centimorgan is a unit used to measure genetic linkage. One centimorgan equals a 1 percent chance that a marker on a chromosome will become separated from a second marker on the same chromosome due to crossing over in a single generation. It translates to approximately 1 million base pairs of DNA sequence in the human genome. The centimorgan is named after the American geneticist Thomas Hunt Morgan.

centriole: Centrioles are paired barrel-shaped organelles located in the cytoplasm of animal cells near the nuclear envelope. Centrioles play a role in organizing microtubules that serve as the cell's skeletal system. They help determine the locations of the nucleus and other organelles within the cell.

centromere: A centromere is a constricted region of a chromosome that separates it into a short arm (p) and a long arm (q). During cell division, the chromosomes first replicate so that each daughter cell receives a complete set of chromosomes. Following DNA replication, the chromosome consists of two identical structures called sister chromatids, which are joined at the centromere.

centrosome: A centrosome is a cellular structure involved in the process of cell division. Before cell division, the centrosome duplicates and then, as division begins, the two centrosomes move to opposite ends of the cell. Proteins called microtubules assemble into a spindle between the two centrosomes and help separate the replicated chromosomes into the daughter cells.

chromatid: A chromatid is one of two identical halves of a replicated chromosome. During cell division, the chromosomes first replicate so that each daughter cell receives a complete set of chromosomes. Following DNA replication, the chromosome consists of two identical structures called sister chromatids, which are joined at the centromere.

chromatin: Chromatin is a substance within a chromosome consisting of DNA and protein. The DNA carries the cell's genetic instructions. The major proteins in chromatin are histones, which help package the DNA in a compact form that fits inside the cell nucleus. Changes in chromatin structure are associated with DNA replication and gene expression.

chromosome: A chromosome is an organized package of DNA found in the nucleus of the cell. Different organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes—22 pairs of numbered chromosomes, called autosomes, and one pair of sex chromosomes, X and Y. Each parent contributes one chromosome to each pair so that offspring get half of their chromosomes from their mother and half from their father.

cloning: Cloning is the process of making identical copies of an organism, cell, or DNA sequence. Molecular cloning is a process by which scientists amplify a desired DNA sequence. The target sequence is isolated, inserted into another DNA molecule (known as a vector), and introduced into a suitable host cell. Then, each time the host cell divides, it replicates the foreign DNA sequence along with its own DNA. Cloning can also refer to asexual reproduction.
**codominance:** Codominance is a relationship between two versions of a gene. Individuals receive one version of a gene, called an allele, from each parent. If the alleles are different, the dominant allele will usually be expressed, while the effect of the other allele, called recessive, is masked. In codominance, however, neither allele is recessive, and the phenotypes of both alleles are expressed.

**codon:** A codon is a trinucleotide sequence of DNA or RNA that corresponds to a specific amino acid. The genetic code describes the relationship between the sequence of DNA bases (A, C, G, and T) in a gene and the corresponding protein sequence that it encodes. The cell reads the sequence of the gene in groups of three bases. There are 64 different codons: 61 specify amino acids, while the remaining three are used as stop signals.

**complex disease:** A complex disease is caused by the interaction of multiple genes and environmental factors. Complex diseases are also called multifactorial. Examples of complex diseases include cancer and heart disease.

**congenital:** Congenital conditions are those present from birth. Birth defects are described as being congenital. They can be caused by a genetic mutation, an unfavorable environment in the uterus, or a combination of both factors.

**contig:** A contig—from the word “contiguous”—is a series of overlapping DNA sequences used to make a physical map that reconstructs the original DNA sequence of a chromosome or a region of a chromosome. A contig can also refer to one of the DNA sequences used in making such a map.

**copy number variation (CNV):** A copy number variation (CNV) is when the number of copies of a particular gene varies from one individual to the next. Following the completion of the Human Genome Project, it became apparent that the genome experiences gains and losses of genetic material. The extent to which CNV contributes to human disease is not yet known. It has long been recognized that some cancers are associated with elevated copy numbers of particular genes.

**crossing over:** Crossing over is the swapping of genetic material that occurs in the germ line. During the formation of egg and sperm cells, also known as meiosis, paired chromosomes from each parent align so that similar DNA sequences from the paired chromosomes cross over one another. Crossing over results in a shuffling of genetic material and is an important cause of the genetic variation seen among offspring.

**cystic fibrosis:** Cystic fibrosis is a hereditary disease characterized by faulty digestion, breathing problems, respiratory infections from mucus buildup, and the loss of salt in sweat. The disease is caused by mutations in a single gene and is inherited as an autosomal recessive trait, meaning that an affected individual inherits two mutated copies of the gene. In the past, cystic fibrosis was almost always fatal in childhood. Today, however, patients commonly live to be 30 years or older.

**cytogeneticist:** A cytogeneticist is a geneticist who specializes in the study of chromosomes and the structure and function of the cell.

**cytogenetics:** Cytogenetics is a branch of genetics that studies the structure and function of the cell and the chromosomes. Early cytogenetic research was accomplished with a standard light microscope. Today, more powerful techniques of analysis, such as fluorescent in situ hybridization (FISH), are commonly used to examine cells and chromosomes.

**cytoplasm:** Cytoplasm is the gelatinous liquid that fills the inside of a cell. It is composed of water, salts, and various organic molecules. Some intracellular organelles, such as the nucleus and mitochondria, are enclosed by membranes that separate them from the cytoplasm.

**cytosine:** Cytosine (C) is one of four chemical bases in DNA, the other three being adenine (A), guanine (G), and thymine (T). Within the DNA molecule, cytosine bases located on one strand form chemical bonds with guanine bases on the opposite strand. The sequence of four DNA bases encodes the cell’s genetic instructions.
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deletion: Deletion is a type of mutation involving the loss of genetic material. It can be small, involving a single missing DNA base pair, or large, involving a piece of a chromosome.

diabetes (diabetes mellitus): Diabetes mellitus is a disease characterized by an inability to make or use the hormone insulin. Insulin is needed by cells to metabolize glucose, the body's main source of chemical energy. Type I diabetes, also called insulin-dependent diabetes mellitus, is usually caused by an autoimmune destruction of insulin-producing cells. Type II diabetes, also called non-insulin-dependent diabetes mellitus, occurs when cells become resistant to the effects of insulin.

diploid: Diploid is a cell or organism that has paired chromosomes, one from each parent. In humans, cells other than human sex cells are diploid and have 23 pairs of chromosomes. Human sex cells (egg and sperm cells) contain a single set of chromosomes and are known as haploid.

DNA (deoxyribonucleic acid): DNA is the chemical name for the molecule that carries genetic instructions in all living things. The DNA molecule consists of two strands that wind around one another to form a shape known as a double helix. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases—adenine (A), cytosine (C), guanine (G), or thymine (T). The two strands are held together by bonds between the bases; adenine bonds with thymine, and cytosine bonds with guanine. The sequence of the bases along the backbones serves as instructions for assembling protein and RNA molecules.

DNA fingerprinting: DNA fingerprinting is a laboratory technique used to establish a link between biological evidence and a suspect in a criminal investigation. A DNA sample taken from a crime scene is compared with a DNA sample from a suspect. If the two DNA profiles are a match, then the evidence came from that suspect. Conversely, if the two DNA profiles do not match, then the evidence cannot have come from the suspect. DNA fingerprinting is also used to establish paternity.

DNA replication: DNA replication is the process by which a molecule of DNA is duplicated. When a cell divides, it must first duplicate its genome so that each daughter cell winds up with a complete set of chromosomes.

DNA sequencing: DNA sequencing is a laboratory technique used to determine the exact sequence of bases (A, C, G, and T) in a DNA molecule. The DNA base sequence carries the information a cell needs to assemble protein and RNA molecules. DNA sequence information is important to scientists investigating the functions of genes. The technology of DNA sequencing was made faster and less expensive as a part of the Human Genome Project.

dominant: Dominant refers to the relationship between two versions of a gene. Individuals receive two versions of each gene, known as alleles, from each parent. If the alleles of a gene are different, one allele will be expressed; it is the dominant gene. The effect of the other allele, called recessive, is masked.

double helix: Double helix is the description of the structure of a DNA molecule. A DNA molecule consists of two strands that wind around each other like a twisted ladder. Each strand has a backbone made of alternating groups of sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases: adenine (A), cytosine (C), guanine (G), or thymine (T). The two strands are held together by bonds between the bases, with adenine forming a base pair with thymine and cytosine forming a base pair with guanine.
Down syndrome (trisomy 21): Down syndrome is a genetic disease resulting from a chromosomal abnormality. An individual with Down syndrome inherits all or part of an extra copy of chromosome 21. Symptoms associated with the syndrome include mental retardation, distinctive facial characteristics, and increased risk for heart defects and digestive problems, which can range from mild to severe. The risk of having a child with Down syndrome rises with the mother's age at the time of conception.

duplication: Duplication is a type of mutation that involves the production of one or more copies of a gene or region of a chromosome. Gene and chromosome duplications occur in all organisms, though they are especially prominent among plants. Gene duplication is an important mechanism of evolution.

electrophoresis: Electrophoresis is a laboratory technique used to separate DNA, RNA, or protein molecules based on their size and electrical charge. An electric current is used to move molecules to be separated through a gel. Pores in the gel work like a sieve, allowing smaller molecules to move faster than larger molecules. The conditions used during electrophoresis can be adjusted to separate molecules in a desired size range.

endoplasmic reticulum (rough): Endoplasmic reticulum is a network of membranes inside a cell through which proteins and other molecules move. Proteins are assembled at organelles called ribosomes. Proteins that will become part of the cell membrane or be exported from the cell are assembled at ribosomes that attach to the endoplasmic reticulum, giving it a rough appearance. Smooth endoplasmic reticulum lacks ribosomes and helps synthesize and concentrate various substances that the cell needs.

enzyme: An enzyme is a biological catalyst and is almost always a protein. It speeds up the rate of a specific chemical reaction in the cell. The enzyme is not destroyed during the reaction and is used over and over. A cell contains thousands of different types of enzyme molecules, each specific to a particular chemical reaction.

epigenetics: Epigenetics is an emerging field of science that studies heritable changes caused by the activation and deactivation of genes without any change in the underlying DNA sequence of the organism. The word epigenetics is of Greek origin and literally means “over” (epi) the genome.

epigenome: The term epigenome is derived from the Greek word epi, which literally means “over” the genome. The epigenome consists of chemical compounds that modify, or mark, the genome in a way that tells it what to do, where to do it, and when to do it. Different cells have different epigenetic marks. These epigenetic marks, which are not part of the DNA itself, can be passed on from cell to cell as cells divide, and from one generation to the next.

epistasis: Epistasis is a circumstance where the expression of one gene is affected by the expression of one or more independently inherited genes. For example, if the expression of gene 2 depends on the expression of gene 1 but gene 1 becomes inactive, then gene 2 will not be expressed. In this example, gene 1 is said to be epistatic to gene 2.

evolution: Evolution is the process by which organisms change over time. Mutations produce genetic variation in populations, and the environment interacts with this variation to select those individuals best adapted to their surroundings. The best-adapted individuals leave behind more offspring than less well-adapted individuals. Given enough time, one species may evolve into many others.
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**exon:** An exon is the portion of a gene that codes for amino acids. In the cells of plants and animals, most gene sequences are broken up by one or more DNA sequences called introns. The parts of the gene sequence that are expressed in the protein are called exons because they are expressed, while the parts of the gene sequence that are not expressed in the protein are called introns because they come in between—or interfere with—the exons.

**family history:** A family history is a record of medical information about an individual and that individual's biological family. Human genetic data are becoming more prevalent and easy to obtain. Increasingly, these data are being used to identify individuals who are at increased risk for developing genetic disorders that run in families.

**first-degree relative:** A first-degree relative is a family member who shares about 50 percent of their genes with a particular individual in a family. First-degree relatives include parents, offspring, and siblings.

**fluorescence in situ hybridization (FISH):** Fluorescence in situ hybridization (FISH) is a laboratory technique for detecting and locating a specific DNA sequence on a chromosome. The technique relies on exposing chromosomes to a small DNA sequence called a probe that has a fluorescent molecule attached to it. The probe sequence binds to its corresponding sequence on the chromosome.

**founder effect:** The founder effect is the reduction in genetic variation that results when a small subset of a large population establishes a new colony. The new population may be very different from the original population, both in terms of its genotypes and phenotypes. In some cases, the founder effect plays a role in the emergence of new species.

**fragile X syndrome:** Fragile X syndrome is a hereditary disorder mostly affecting males. Symptoms include mental retardation, distinctive facial features, and poor muscle tone. The syndrome is caused by mutations in a gene on the X chromosome. Since males have a single copy of the X chromosome, they show symptoms if that gene on their X chromosome is mutated. Females have a second, usually normal, copy of the gene on their other X chromosome. Consequently, they are less likely to show symptoms of the syndrome.

**frameshift mutation:** A frameshift mutation is a type of mutation involving the insertion or deletion of a nucleotide in which the number of deleted base pairs is not divisible by three. “Divisible by three” is important because the cell reads a gene in groups of three bases. Each group of three bases corresponds to 1 of 20 different amino acids used to build a protein. If a mutation disrupts this reading frame, then the entire DNA sequence following the mutation will be read incorrectly.

**fraternal twins:** Fraternal twins are also called dizygotic twins. They result from the fertilization of two separate eggs during the same pregnancy. Fraternal twins may be of the same or different sexes. They share half their genes, just like any other siblings. In contrast, twins that result from the fertilization of a single egg that then splits in two are called monozygotic, or identical, twins. Identical twins share all their genes and are always the same sex.

**gene:** The gene is the basic physical unit of inheritance. Genes are passed from parents to offspring and contain the information needed to specify traits. Genes are arranged, one after another, on structures called chromosomes. A chromosome contains a single, long DNA molecule, only a portion of which corresponds to a single gene. Humans have about 23,000 genes on their chromosomes.

**gene amplification:** Gene amplification is an increase in the number of copies of a gene sequence. Cancer cells sometimes produce multiple copies of genes in response to signals from other cells or their environment. The term can also refer to polymerase chain reaction (PCR), a laboratory technique scientists use to amplify gene sequences in a test tube.
**gene-environment interaction**: Gene-environment interaction is an influence on the expression of a trait that results from the interplay between genes and the environment. Some traits are strongly influenced by genes, while others are strongly influenced by the environment. Most traits, however, are influenced by one or more genes interacting in complex ways with the environment.

**gene expression**: Gene expression is the process by which the information encoded in a gene is used to direct the assembly of a protein molecule. The cell reads the sequence of the gene in groups of three bases. Each group of three bases (codon) corresponds to 1 of 20 different amino acids used to build the protein.

**gene mapping**: Gene mapping is the process of establishing the locations of genes on the chromosomes. Early gene maps used linkage analysis. The closer two genes are to each other on the chromosome, the more likely it is that they will be inherited together. By following inheritance patterns, the relative positions of genes can be determined. More recently, scientists have used recombinant DNA (rDNA) techniques to establish the actual physical locations of genes on the chromosomes.

**gene pool**: A gene pool is the total genetic diversity found within a population or a species. A large gene pool has extensive genetic diversity and is better able to withstand the challenges posed by environmental stresses. Inbreeding contributes to the creation of a small gene pool and makes populations or species more likely to go extinct when faced with some type of stress.

**gene regulation**: Gene regulation is the process of turning genes on and off. During early development, cells begin to take on specific functions. Gene regulation ensures that the appropriate genes are expressed at the proper times. Gene regulation can also help an organism respond to its environment. Gene regulation is accomplished by a variety of mechanisms including chemically modifying genes and using regulatory proteins to turn genes on or off.

**gene therapy**: Gene therapy is an experimental technique for treating disease by altering the patient's genetic material. Most often, gene therapy works by introducing a healthy copy of a defective gene into the patient's cells.

**genetic code**: The genetic code is the instructions in a gene that tell the cell how to make a specific protein. A, C, G, and T are the “letters” of the DNA code; they stand for the chemicals adenine (A), cytosine (C), guanine (G), and thymine (T), 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**: Genetic counseling is the professional interaction between a healthcare provider with specialized knowledge of genetics and an individual or family. The genetic counselor determines whether a condition in the family may be genetic and estimates the chances that another relative may be affected. Genetic counselors also offer and interpret genetic tests that may help to estimate risk of disease. The genetic counselor conveys information in an effort to address concerns of the client and provides psychological counseling to help families adapt to their condition or risk.

**genetic discrimination**: Genetic discrimination is prejudice directed against people who have or may have a genetic disease. Genetic discrimination can involve being denied employment or health insurance. In a healthcare context, it can refer to people being treated based on their genetic status rather than by some more relevant criterion.

**genetic drift**: Genetic drift is a mechanism of evolution. It refers to random fluctuations in the frequencies of alleles from generation to generation due to chance events. Genetic drift can cause traits to be dominant or to disappear from a population. The effects of genetic drift are most pronounced in small populations.
**Human Genetic Variation**

**genetic engineering:** Genetic engineering is the process of using recombinant DNA (rDNA) technology to alter the genetic makeup of an organism. Traditionally, humans have manipulated genomes indirectly by controlling breeding and selecting offspring with desired traits. Genetic engineering involves the direct manipulation of one or more genes. Most often, a gene from another species is added to an organism’s genome to give it a desired phenotype.

**genetic epidemiology:** Genetic epidemiology is a relatively new medical discipline that seeks to understand how genetic factors interact with the environment in the context of disease in populations. Areas of study include the causes, distribution, and control of inherited disease.

**genetic imprinting:** In genetic imprinting, the ability of a gene to be expressed depends on the sex of the parent who passed on the gene. In some cases, imprinted genes are expressed when they are inherited from the mother. In other cases, they are expressed when inherited from the father. Unlike genetic mutations that can affect the ability of inherited genes to be expressed, genetic imprinting does not affect the DNA sequence itself. Genetic imprinting affects gene expression by chemically modifying DNA and/or altering the chromatin structure. Often, genetic imprinting results in a gene being expressed only in the chromosome inherited from one or the other parent. Although this is a normal process, when it combines with genetic mutations, disease can result. For example, Prader-Willi syndrome and Angelman syndrome are two distinct diseases caused by a deletion in the same part of chromosome 15. When this deletion occurs on the chromosome 15 that came from the father, the child will have Prader-Willi syndrome. However, when the deletion occurs on the chromosome 15 that came from the mother, the child will develop Angelman syndrome. This occurs because genes located in this region undergo genetic imprinting.

**Genetic Information Nondiscrimination Act (GINA):** This federal legislation that makes it unlawful to use genetic profiles to discriminate against individuals in matters related to health insurance and employment. These protections are intended to encourage Americans to take advantage of genetic testing as part of their medical care. President George W. Bush signed GINA into law on May 22, 2008.

**genetic map:** A genetic map is a type of chromosome map that shows the relative locations of genes and other important features. The map is based on the idea of linkage, which means that the closer two genes are to each other on the chromosome, the greater the probability that they will be inherited together. By following inheritance patterns, the relative locations of genes along the chromosome are established.

**genetic marker:** A genetic marker is a DNA sequence with a known physical location on a chromosome. Genetic markers can help link an inherited disease with the responsible gene. DNA segments close to each other on a chromosome tend to be inherited together. Genetic markers are used to track the inheritance of a nearby gene that has not yet been identified but whose approximate location is known. The genetic marker itself may be a part of a gene or may have no known function.

**genetic screening:** Genetic screening is the process of testing a population for a genetic disease in order to identify a subgroup of individuals who either have the disease or the potential to pass it on to their offspring.

**genetic testing:** Genetic testing is the use of a laboratory test to look for genetic variations associated with a disease. The results of a genetic test can be used to confirm or rule out a suspected genetic disease or to determine the likelihood that a person will pass on a mutation to offspring. Genetic testing may be performed prenatally or after birth. Ideally, a person who undergoes a genetic test will discuss the meaning of the test and its results with a genetic counselor.
**genetic variation**: Genetic variation refers to diversity in gene frequencies. Genetic variation can refer to differences between individuals or to differences between populations. Mutation is the ultimate source of genetic variation, but mechanisms such as sexual reproduction and genetic drift contribute to it as well.

**genome**: The genome is the entire set of genetic instructions in a cell. In humans, the genome consists of 23 pairs of chromosomes, found in the nucleus, as well as a small chromosome found in the cell's mitochondria. These chromosomes, taken together, contain approximately 3.1 billion bases of DNA sequence.

**genomic**: Genomics refers to the study of the entire genome of an organism, whereas genetics refers to the study of a particular gene.

**genotype**: A genotype is an individual's collection of genes. The term can also refer to the two alleles inherited for a particular gene. The genotype is expressed when the information encoded in the genes' DNA is used to make protein and RNA molecules. The expression of the genotype contributes to the individual's observable traits, called the phenotype.

**germ line**: A germ line is the sex cells (eggs and sperm) that are used by sexually reproducing organisms to pass on genes from generation to generation. Egg and sperm cells are called germ cells, in contrast to the other cells of the body, which are called somatic cells.

**Golgi body**: A Golgi body, also known as a Golgi apparatus, is a cell organelle that helps process and package proteins and lipid molecules, especially proteins destined to be exported from the cell. Named after its discoverer, Camillo Golgi, the Golgi body appears as a series of stacked membranes.

**guanine**: Guanine (G) is one of four chemical bases in DNA, with the other three being adenine (A), cytosine (C), and thymine (T). Within the DNA molecule, guanine bases located on one strand form chemical bonds with cytosine bases on the opposite strand. The sequence of four DNA bases encodes the cell's genetic instructions.

**haploid**: Haploid is the quality of a cell or organism having a single set of chromosomes. Organisms that reproduce asexually are haploid. Sexually reproducing organisms are diploid (having two sets of chromosomes, one from each parent). In humans, only their egg and sperm cells are haploid.

**haplotype**: A haplotype is a set of DNA variations, or polymorphisms, that tend to be inherited together. A haplotype can refer to a combination of alleles or to a set of single nucleotide polymorphisms (SNPs) found on the same chromosome. Information about haplotypes is being collected by the International HapMap Project and is used to investigate the influence of genes on disease.

**HapMap**: HapMap (short for “haplotype map”) is the nickname of the International HapMap Project, an international project that seeks to relate variations in human DNA sequences with genes associated with health. A haplotype is a set of DNA variations, or polymorphisms, that tend to be inherited together. A haplotype can refer to a combination of alleles or to a set of single nucleotide polymorphisms (SNPs) found on the same chromosome. The HapMap describes common patterns of genetic variation among people.
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**hemophilia:** Hemophilia is an inherited disease, most commonly affecting males, that is characterized by a deficiency in blood clotting. The responsible gene is located on the X chromosome, and since males inherit only one copy of the X chromosome, if that chromosome carries the mutated gene, then they will have the disease. Females have a second, usually normal, copy of the gene on their other X chromosome, so they can pass on the disease without experiencing its symptoms.

**heterozygous:** Heterozygous refers to having inherited different forms, or alleles, of a particular gene from each parent. A heterozygous genotype stands in contrast to a homozygous genotype, where an individual inherits identical forms of a particular gene from each parent.

**histone:** A histone is a protein that provides structural support to a chromosome. By wrapping around complexes of histone proteins, very long DNA molecules can fit into the cell nucleus and give the chromosome a more compact shape. Some variants of histones are associated with the regulation of gene expression.

**holoprosencephaly:** Holoprosencephaly is a developmental disorder that results when the forebrain of the embryo fails to divide and form the right and left halves of the brain. The disorder produces a single-lobed brain structure and severe skull and facial abnormalities. The deformities often cause babies to die before birth. In mild cases, babies are born with near-normal brain development and facial abnormalities involving cleft lip or cleft palate.

**homozygous:** Homozygous is a genetic condition where an individual inherits the same form, or allele, for a particular gene from both parents.

**Human Genome Project:** The Human Genome Project was an international project that mapped and sequenced the entire human genome. Completed in April 2003, data from the project are freely available to researchers and others interested in genetics and human health.

**Huntington’s disease:** Huntington’s disease is an inherited disease characterized by the progressive loss of brain and muscle function. Symptoms usually begin during middle age. The disease is inherited as an autosomal dominant trait, meaning that a single mutated copy of the responsible gene is sufficient to cause the disease.

**hybridization:** Hybridization is the process of combining two complementary single-stranded DNA or RNA molecules and allowing them to form a single double-stranded molecule through base pairing. In a reversal of this process, a double-stranded DNA (or RNA, or DNA/RNA) molecule can be heated to break the base pairing and separate the two strands. Hybridization is a part of many important laboratory techniques such as polymerase chain reaction and Southern blotting.

**identical twins:** Identical twins are also known as monozygotic twins. They result from the fertilization of a single egg that splits in two. Identical twins share all of their genes and are always of the same sex. In contrast, fraternal, or dizygotic, twins result from the fertilization of two separate eggs during the same pregnancy. They share half their genes, just like any other siblings. Fraternal twins can be of the same or different sexes.

**homologous recombination:** Homologous recombination is a type of genetic recombination that occurs during meiosis (the formation of egg and sperm cells). Paired chromosomes from the male and female parent align so that similar DNA sequences from the paired chromosomes cross over each other. Crossing over results in a shuffling of genetic material and is an important cause of the genetic variation seen among offspring.

**in situ hybridization:** In situ hybridization is a laboratory technique in which a single-stranded DNA or RNA sequence called a probe is allowed to form complementary base pairs with DNA or RNA present in a tissue or chromosome sample. The probe has a chemical or radioactive label attached to it so that its binding can be observed.
**inherited**: An inherited trait is one that is genetically determined. Inherited traits are passed from parent to offspring according to the rules of Mendelian genetics. Most traits are not strictly determined by genes, but rather are influenced by both genes and environment.

**insertion**: Insertion is a type of mutation involving the addition of genetic material. An insertion mutation can be small, involving a single extra DNA base pair, or large, involving a piece of a chromosome.

**intron**: An intron is a portion of a gene that does not code for amino acids. In the cells of plants and animals, most gene sequences are broken up by one or more introns. The parts of the gene sequence that are expressed in the protein are called exons because they are expressed, while the parts of the gene sequence that are not expressed in the protein are called introns because they come in between the exons.

**karyotype**: A karyotype is an individual’s collection of chromosomes. The term also refers to a laboratory technique that produces an image of an individual’s chromosomes. The karyotype is used to look for abnormal numbers or structures of chromosomes.

**knockout**: A knockout typically refers to an organism that has been genetically engineered to lack one or more specific genes. Scientists create knockouts (often in mice) so that they can study the impact of the missing genes and learn something about the genes’ function.

**linkage**: Linkage is the close association of genes or other DNA sequences on the same chromosome. The closer two genes are to each other on the chromosome, the greater the probability that they will be inherited together.

**locus**: A locus is the specific physical location of a gene or other DNA sequence on a chromosome, like a genetic street address. The plural of locus is “loci.”

**LOD score**: LOD stands for “logarithm of the odds.” In genetics, the LOD score is a statistical estimate of whether two genes, or a gene and a disease gene, are likely to be located near each other on a chromosome and are therefore likely to be inherited together. A LOD score of 3 or higher is generally understood to mean that two genes are located close to each other. In terms of significance, a LOD score of 3 means the odds are 1,000 to 1 that the two genes are linked and, therefore, inherited together.

**lymphocyte**: A lymphocyte is a type of white blood cell that is part of the immune system. There are two main types of lymphocytes: B cells and T cells. The B cells produce antibodies that attack invading bacteria, viruses, and toxins. The T cells destroy the body’s own cells that have themselves been taken over by viruses or become cancerous.

**lyonization**: Lyonization is commonly known as X-inactivation. In mammals, males receive one copy of the X chromosome while females receive two copies. To prevent female cells from having twice as many gene products from the X chromosomes as males, one copy of the X chromosome in each female cell is inactivated. In placental mammals, the choice of which X chromosome is inactivated is random, whereas in marsupials, it is always the paternal copy that is inactivated.

**lysosome**: A lysosome is a membrane-bound cell organelle that contains digestive enzymes. Lysosomes are involved with various cell processes. They break down excess or worn-out cell parts. They may be used to destroy invading viruses and bacteria. If the cell is damaged beyond repair, lysosomes can help it self-destruct in a process called programmed cell death, or apoptosis.
**mapping**: Mapping is the process of making a representative diagram cataloging the genes and other features of a chromosome and showing their relative locations. Cytogenetic maps are made using photomicrographs of chromosomes stained to reveal structural variations. Genetic maps use the idea of linkage to estimate the relative locations of genes. Physical maps, made using recombinant DNA (rDNA) technology, show the actual physical locations of landmarks along a chromosome.

**marker**: A marker is a DNA sequence with a known physical location on a chromosome. Markers can help link an inherited disease with the responsible genes. DNA segments close to each other on a chromosome tend to be inherited together. Markers are used to track the inheritance of a nearby gene that has not yet been identified but whose approximate location is known. The marker itself may be a part of a gene or may have no known function.

**meiosis**: Meiosis is the formation of egg and sperm cells. In sexually reproducing organisms, body cells are diploid, meaning they contain two sets of chromosomes (one set from each parent). To maintain this state, the egg and sperm that unite during fertilization are haploid, meaning they each contain a single set of chromosomes. During meiosis, diploid cells undergo DNA replication followed by two rounds of cell division, producing four haploid sex cells.

**Mendel, Johann (Gregor)**: Gregor Mendel was an Austrian monk who in the 19th century worked out the basic laws of inheritance, even before the term “gene” had been coined. In his monastery garden, Mendel performed thousands of crosses with garden peas. Mendel explained his results by describing two laws of inheritance that introduced the idea of dominant and recessive traits.

**Mendelian inheritance**: Mendelian inheritance refers to patterns of inheritance of organisms that reproduce sexually. The Austrian monk Gregor Mendel performed thousands of crosses with garden peas at his monastery during the middle of the 19th century. Mendel explained his results by describing two laws of inheritance that introduced the idea of dominant and recessive genes.

**messenger RNA (mRNA)**: Messenger RNA (mRNA) is a single-stranded RNA molecule that is complementary to one of the DNA strands of a gene. The mRNA is an RNA version of the gene that leaves the cell nucleus and moves to the cytoplasm where proteins are made. During protein synthesis, an organelle called a ribosome moves along the mRNA, reads its base sequence, and uses the genetic code to translate each three-base triplet, or codon, into its corresponding amino acid.

**metagenomics**: Metagenomics is the study of a collection of genetic material (genomes) from a mixed community of organisms. Metagenomics usually refers to the study of microbial communities.

**metaphase**: Metaphase is a stage during the process of cell division (mitosis or meiosis). Usually, individual chromosomes cannot be observed in the cell nucleus. However, during metaphase of mitosis or meiosis, the chromosomes condense and become distinguishable as they align in the center of the dividing cell. Metaphase chromosomes are used during the karyotyping procedure used to look for chromosomal abnormalities.

**microarray technology**: Microarray technology is a developing technology used to study the expression of many genes at once. It involves placing thousands of gene sequences in known locations on a glass slide called a gene chip. A sample containing DNA or RNA is placed in contact with the gene chip. Complementary base pairing between the sample and the gene sequences on the chip produces light that is measured. Areas on the chip producing light identify genes expressed in the sample.
**microbiome**: A microbiome is all of the genetic material found within an individual microbe such as a bacterium, fungal cell, or virus. It also may refer to the collection of genetic material found in a community of microbes that live together.

**microsatellite**: Microsatellite sequences are repetitive DNA sequences usually several base pairs in length. Microsatellite sequences are composed of noncoding DNA and are not parts of genes. They are used as genetic markers to follow the inheritance of genes in families.

**missense mutation**: A missense mutation is when the change of a single base pair causes the substitution of a different amino acid in the resulting protein. This amino acid substitution may have no effect, or it may render the protein nonfunctional.

**mitochondria**: Mitochondria are membrane-bound cell organelles (mitochondrion, singular) that generate most of the chemical energy needed to power the cell's biochemical reactions. Chemical energy produced by the mitochondria is stored in a small molecule called adenosine triphosphate (ATP). Mitochondria contain their own small chromosome(s). Generally, mitochondria, and therefore mitochondrial DNA, are inherited only from the mother.

**mitochondrial DNA**: Mitochondrial DNA is the small circular chromosome found inside mitochondria. Mitochondria are the organelles in cells where energy is produced. The mitochondria, and thus mitochondrial DNA, are passed from mother to offspring.

**mitosis**: Mitosis is a cellular process that replicates chromosomes and produces two identical nuclei in preparation for cell division. Generally, mitosis is immediately followed by the equal division of the cell nuclei and other cell contents into two daughter cells.

**monosomy**: Monosomy is the state of having a single copy of a chromosome pair instead of the usual two copies found in diploid cells. Monosomy can be partial if a portion of the second chromosome copy is present. Monosomy, or partial monosomy, is the cause of some human diseases such as Turner syndrome and Cri du Chat syndrome.

**mouse model**: A mouse model is a laboratory mouse used to study some aspect of human physiology or disease. A variety of different model organisms are used in this regard, but mice are especially useful because they share mammalian features with humans and suffer from many of the same diseases. A large number of mouse models have been created by selective breeding and genetic engineering to target specific human diseases.

**mutagen**: A mutagen is a chemical or physical phenomenon, such as ionizing radiation, that promotes errors in DNA replication. Exposure to a mutagen can produce DNA mutations that cause or contribute to diseases such as cancer.

**mutation**: A mutation is a change in a DNA sequence. Mutations can result from DNA copying mistakes made during cell division, exposure to ionizing radiation, exposure to chemicals called mutagens, or infection by viruses. Germ line mutations occur in eggs and sperm and can be passed on to offspring, while somatic mutations occur in body cells and are not passed on.

**nanotechnology**: Nanotechnology is the science of manipulating matter on the atomic and molecular scales to solve problems. Nanotechnology is a developing applied science that has the potential to make significant contributions to many fields, including engineering, computer science, and medicine.

**newborn screening**: Newborn screening is testing performed on newborn babies to detect a wide variety of disorders. Typically, testing is performed on a blood sample obtained from a heel prick when the baby is two or three days old. In the United States, newborn screening is mandatory for several different genetic disorders, though the exact set of required tests differs from state to state.
**noncoding DNA:** Noncoding DNA sequences do not code for amino acids. Most noncoding DNA lies between genes on the chromosome and has no known function. Other noncoding DNA, called introns, is found within genes. Some noncoding DNA plays a role in the regulation of gene expression.

**nondirectiveness:** Nondirectiveness refers to the nature of the genetic counseling process. According to the principle of nondirectiveness, the genetic counselor has the responsibility to provide the client with accurate information about a test or outcome but should remain neutral and not try to influence the decisions made by the client.

**nonsense mutation:** A nonsense mutation is the substitution of a single base pair that leads to the appearance of a stop codon where previously there was a codon specifying an amino acid. The presence of this premature stop codon results in the production of a shortened, and likely nonfunctional, protein.

**northern blot:** Northern blot is a laboratory technique used to detect a specific RNA sequence in a blood or tissue sample. The sample RNA molecules are separated by size using gel electrophoresis. The RNA fragments are transferred out of the gel to the surface of a membrane. The membrane is exposed to a DNA probe labeled with a radioactive or chemical tag. If the probe binds to the membrane, then the complementary RNA sequence is present in the sample.

**nucleic acid:** Nucleic acids are an important class of macromolecules found in all cells and viruses. The functions of nucleic acids have to do with the storage and expression of genetic information. Deoxyribonucleic acid (DNA) encodes the information the cell needs to make proteins. A related type of nucleic acid, called ribonucleic acid (RNA), comes in different molecular forms that participate in protein synthesis.

**nucleolus:** The nucleolus is a region found within the cell nucleus concerned with producing and assembling the cell's ribosomes. Following assembly, ribosomes are transported to the cell cytoplasm, where they serve as the sites for protein synthesis.

**nucleopore:** A nucleopore is one of a series of small holes found in the nuclear membrane. The nucleopore serves as a channel for transporting nucleic acids and proteins into and out of the cell nucleus.

**nucleosome:** A nucleosome is the basic repeating unit of eukaryotic chromatin. In a human cell, about six feet of DNA must be packaged into a nucleus with a diameter less than a human hair. A single nucleosome consists of about 150 base pairs of DNA sequence wrapped around a core of histone proteins. The nucleosomes are arranged like beads on a string. They are repeatedly folded in on themselves to form a chromosome.

**nucleotide:** A nucleotide is the basic building block of nucleic acids. RNA and DNA are polymers made of long chains of nucleotides. A nucleotide consists of a sugar molecule (either ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen-containing base. The bases used in DNA are adenine (A), cytosine (C), guanine (G), and thymine (T). In RNA, the base uracil (U) takes the place of thymine.
nucleus: A nucleus is a membrane-bound organelle that contains the cell's chromosomes. Pores in the nuclear membrane allow molecules to pass into and out of the nucleus.

oncogene: An oncogene is a mutated gene that contributes to the development of a cancer. In their normal, unmutated state, oncogenes are called proto-oncogenes, and they play roles in the regulation of cell division. Some oncogenes work like putting your foot down on the accelerator of a car, pushing a cell to divide. Other oncogenes work like removing your foot from the brake while parked on a hill, also causing the cell to divide.

open reading frame: An open reading frame is a portion of a DNA molecule that, when translated into amino acids, contains no stop codons. The genetic code reads DNA sequences in groups of three base pairs, which means that a double-stranded DNA molecule can read in any of six possible reading frames—three in the forward direction and three in the reverse. A long open reading frame is likely part of a gene.

organ: In biology, an organ (from the Latin "organum," meaning an instrument or tool) is a collection of tissues that structurally form a functional unit specialized to perform a particular function. Your heart, kidneys, and lungs are examples of organs.

organelle: An organelle is a subcellular structure that has one or more specific jobs to perform in the cell, much like an organ does in the body. Among the more important cell organelles are the nuclei, which store genetic information; mitochondria, which produce chemical energy; and ribosomes, which assemble proteins.

pedigree: A pedigree is a genetic representation of a family tree that diagrams the inheritance of a trait or disease though several generations. The pedigree shows the relationships between family members and indicates which individuals express or silently carry the trait in question.

peptide: A peptide is one or more amino acids linked by chemical bonds. The term also refers to the type of chemical bond that joins the amino acids together. A series of linked amino acids is a polypeptide. The cell's proteins are made from one or more polypeptides.

personalized medicine: Personalized medicine is an emerging practice of medicine that uses an individual's genetic profile to guide decisions about the prevention, diagnosis, and treatment of disease. Knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen. Personalized medicine is being advanced through data from the Human Genome Project.

pharmacogenomics: Pharmacogenomics is a branch of pharmacology concerned with using DNA and amino acid sequence data to inform drug development and testing. An important application of pharmacogenomics is correlating individual genetic variation with drug responses.

phenotype: A phenotype is an individual's observable traits, such as height, eye color, and blood type. The genetic contribution to the phenotype is called the genotype. Some traits are largely determined by the genotype, while others are largely determined by environmental factors.

phosphate backbone: A phosphate backbone is the portion of the DNA double helix that provides structural support to the molecule. DNA consists of two strands that wind around each other like a twisted ladder. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases—adenine (A), cytosine (C), guanine (G), or thymine (T). The two strands are held together by bonds between the bases, with adenine forming a base pair with thymine and cytosine forming a base pair with guanine.
**physical map**: A physical map of a chromosome or a genome shows the physical locations of genes and other DNA sequences of interest. Physical maps are used to help scientists identify and isolate genes by positional cloning.

**plasma membrane (cell membrane)**: The plasma membrane, also called the cell membrane, is the membrane found in all cells that separates the interior of the cell from the outside environment. In bacterial and plant cells, a cell wall is attached to the plasma membrane on its outside surface. The plasma membrane consists of a lipid bilayer that is semipermeable. The plasma membrane regulates the transport of materials entering and exiting the cell.

**plasmid**: A plasmid is a small, often circular DNA molecule found in bacteria and other cells. Plasmids are separate from the bacterial chromosome and replicate independently of it. They generally carry only a small number of genes, notably some associated with antibiotic resistance. Plasmids may be passed between different bacterial cells.

**point mutation**: A point mutation is when a single base pair is altered. Point mutations can have one of three effects. First, the base substitution can be a silent mutation, where the altered codon corresponds to the same amino acid. Second, the base substitution can be a missense mutation, where the altered codon corresponds to a different amino acid. Or third, the base substitution can be a nonsense mutation, where the altered codon corresponds to a stop signal.

**polydactyly**: Polydactyly is an abnormality characterized by extra fingers or toes. The condition may be present as part of a collection of abnormalities, or it may exist by itself. When by itself, it is inherited as an autosomal dominant trait.

**polygenetic trait**: A polygenetic trait is one whose phenotype is influenced by more than one gene. Traits that display a continuous distribution, such as height or skin color, are polygenic. The inheritance of polygenic traits does not show the phenotypic ratios characteristic of Mendelian inheritance, though each of the genes contributing to the trait is inherited as described by Gregor Mendel. Many polygenic traits are also influenced by the environment and are called multifactorial.

**polymerase chain reaction (PCR)**: Polymerase chain reaction (PCR) is a laboratory technique used to amplify DNA sequences. The method involves using short DNA sequences called primers to select the portion of the genome to be amplified. The temperature of the sample is repeatedly raised and lowered to help a DNA replication enzyme copy the target DNA sequence. The technique can produce a billion copies of the target sequence in just a few hours.

**polymorphism**: Polymorphism involves one of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair. Polymorphisms can also be much larger and involve long stretches of DNA. Scientists are studying how single nucleotide polymorphisms, or SNPs (pronounced “snips”), in the human genome correlate with disease, drug response, and other phenotypes.

**population genomics**: Population genomics is the application of genomic technologies to understand populations of organisms. In humans, population genomics typically refers to applying technology in the quest to understand how genes contribute to our health and well-being.
positional cloning: Positional cloning is a laboratory technique used to locate the position of a disease-associated gene along the chromosome. This approach works even when little or no information is available about the biochemical basis of the disease. Positional cloning is used in conjunction with linkage analysis. It involves the isolation of partially overlapping DNA segments that progress along the chromosome toward a candidate gene.

primer: A primer is a short, single-stranded DNA sequence used in the polymerase chain reaction (PCR) technique. In the PCR method, a pair of primers is used to hybridize with the sample DNA and define the region of the DNA that will be amplified. Primers are also referred to as oligonucleotides.

proband: A proband is an individual being studied or reported on. A proband is usually the first affected individual in a family who brings a genetic disorder to the attention of the medical community.

probe: A probe is a single-stranded sequence of DNA or RNA used to search for its complementary sequence in a sample genome. The probe is placed into contact with the sample under conditions that allow the probe to hybridize with its complementary sequence. The probe is labeled with a radioactive or chemical tag that allows its binding to be visualized. In a similar way, labeled antibodies are used to probe a sample for the presence of a specific protein.

progeria: Progeria is a rare disease characterized by accelerated aging. The classic form of progeria is called Hutchinson-Gilford progeria syndrome (HGPS), named for the doctors who first described it. Progeria is caused by a mutation in the gene for LMNA (pronounced “Lamin A”). The LMNA protein provides structural support to the cell nucleus. When the gene is mutated, the LMNA protein produces nuclear instability that leads to premature aging. Affected persons commonly die from heart disease during late childhood.

promoter: A promoter is a sequence of DNA needed to turn a gene on or off. The process of transcription is initiated at the promoter. Usually found near the beginning of a gene, the promoter has a binding site for the enzyme used to make a messenger RNA (mRNA) molecule.

prostate cancer: Prostate cancer is a disease characterized by uncontrolled cell growth in the prostate gland, which is part of the male reproductive system. Prostate cancer generally affects men over the age of 50. It is responsible for more deaths among men than any other cancer except lung cancer.

protein: Proteins are an important class of molecules found in all living cells. A protein is composed of one or more long chains of amino acids, the sequence of which corresponds to the DNA sequence of the gene that encodes it. Proteins play a variety of roles in the cell, including structural (cytoskeleton), mechanical (muscle), biochemical (enzymes), and cell signaling (hormones). Proteins are also an essential part of diet.

pseudogene: A pseudogene is a DNA sequence that resembles a gene but has been mutated into an inactive form over the course of evolution. A pseudogene shares an evolutionary history with a functional gene and can provide insight into their shared ancestry.

race: Race is a fluid concept used to group people according to various factors, including ancestral background and social identity. Race is also used to group people that share a set of visible characteristics, such as skin color and facial features. Though these visible traits are influenced by genes, the vast majority of genetic variation exists within racial groups and not between them. Race is an ideology, and for this reason, many scientists believe that race should be more accurately described as a social construct and not a biological one.
**Human Genetic Variation**

**recessive**: Recessive is a quality found in the relationship between two versions of a gene. Individuals receive one version of a gene, called an allele, from each parent. If the alleles are different, the dominant allele will be expressed, while the effect of the other allele, called recessive, is masked. In the case of a recessive genetic disorder, an individual must inherit two copies of the mutated allele for the disease to be present.

**recombinant DNA (rDNA)**: Recombinant DNA (rDNA) is a technology that uses enzymes to cut and paste together DNA sequences of interest. The recombined DNA sequences can be placed into vehicles called vectors that ferry the DNA into a suitable host cell where it can be copied or expressed.

**repressor**: A repressor is a protein that turns off the expression of one or more genes. The repressor protein works by binding to the gene’s promoter region, preventing the production of messenger RNA (mRNA).

**restriction enzyme**: A restriction enzyme is an enzyme isolated from bacteria that cuts DNA molecules at specific sequences. The isolation of these enzymes was critical to the development of recombinant DNA (rDNA) technology and genetic engineering.

**restriction fragment length polymorphism (RFLP)**: Restriction fragment length polymorphism (RFLP) is a type of polymorphism that results from variation in the DNA sequence recognized by restriction enzymes. These are bacterial enzymes that scientists use to cut DNA molecules at known locations. RFLPs (pronounced “rif lips”) are used as markers on genetic maps. Typically, gel electrophoresis is used to visualize RFLPs.

**retrovirus**: A retrovirus is a virus that uses RNA as its genetic material. When a retrovirus infects a cell, it makes a DNA copy of its genome that is inserted into the DNA of the host cell. A variety of different retroviruses causes human diseases such as AIDS and some forms of cancer.

**ribosome**: A ribosome is a cellular particle made of RNA and protein that serves as the site for protein synthesis in the cell. The ribosome reads the sequence of the messenger RNA (mRNA) and, using the genetic code, translates the sequence of RNA bases into a sequence of amino acids.

**risk**: Risk, in the context of genetics, refers to the probability that an individual will be affected by a particular genetic disorder. Genes and environment both influence risk. Some individuals’ risk may be higher because they inherit genes that cause or increase susceptibility to a disorder. Other individuals may be at higher risk because they live or work in an environment that promotes the development of the disorder.

**RNA (ribonucleic acid)**: Ribonucleic acid (RNA) is a molecule similar to DNA. Unlike DNA, RNA is single-stranded. An RNA strand has a backbone made of alternating sugar (ribose) and phosphate groups. Attached to each sugar is one of four bases—adenine (A), uracil (U), cytosine (C), or guanine (G). Different types of RNA exist in the cell: messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). More recently, some small RNAs have been found to be involved in regulating gene expression.

**sex chromosome**: A sex chromosome is a type of chromosome that participates in sex determination. Humans and most other mammals have two sex chromosomes, the X and the Y. Females have two X chromosomes in their cells, while males have both an X and a Y chromosome in their cells. Egg cells all contain an X chromosome, while sperm cells contain an X or a Y chromosome. This means that during fertilization, the male determines the sex of the offspring.
**sex-linked**: Sex-linked is a trait in which a gene is located on a sex chromosome. In humans, the term generally refers to traits influenced by genes on the X chromosome. This is because the X chromosome is large and contains many more genes than the smaller Y chromosome. In a sex-linked disease, it is usually males who are affected because they have a single copy of the X chromosome that carries the mutation. In females, the effect of the mutation may be masked by the second copy of the X chromosome.

**shotgun sequencing**: Shotgun sequencing is a laboratory technique for determining the DNA sequence of an organism’s genome. The method involves breaking the genome into a collection of small DNA fragments that are sequenced individually. A computer program looks for overlaps in the DNA sequences and uses them to place the individual fragments in their correct order to reconstitute the genome.

**sickle cell disease**: Sickle cell disease is a hereditary disease seen most often among people of African ancestry. Caused by mutations in one of the genes that encode the hemoglobin protein, the disease is inherited as an autosomal recessive trait. The mutation causes the red blood cells to take on an unusual sickle shape. Individuals affected by sickle cell disease are chronically anemic and experience significant damage to their heart, lungs, and kidneys.

**single nucleotide polymorphisms (SNPs)**: Single nucleotide polymorphisms (SNPs) are a type of polymorphism involving variation of a single base pair. Scientists are studying how single nucleotide polymorphisms, or SNPs (pronounced “snips”), in the human genome correlate with disease, drug response, and other phenotypes.

**somatic cells**: A somatic cell is any cell of the body except sperm and egg cells. Somatic cells are diploid, meaning that they contain two sets of chromosomes, one from each parent. Mutations in somatic cells can affect the individual, but they are not passed on to offspring.

**Southern blot**: Southern blotting is a laboratory technique used to detect a specific DNA sequence in a blood or tissue sample. A restriction enzyme is used to cut a sample of DNA into fragments that are separated using gel electrophoresis. The DNA fragments are transferred out of the gel to the surface of a membrane. The membrane is exposed to a DNA probe labeled with a radioactive or chemical tag. If the probe binds to the membrane, then the probe sequence is present in the sample.

**spectral karyotype (SKY)**: Spectral karyotype (SKY) is a karyotype in which the homologous pairs of chromosomes are manipulated in such a way that they have distinctive colors. The SKY technique makes it easier for scientists to detect chromosomal abnormalities than they can with a conventional karyotype.

**stem cell**: A stem cell is a cell with the potential to form many of the different cell types found in the body. When stem cells divide, they can form more stem cells or other cells that perform specialized functions. Embryonic stem cells have the potential to form a complete individual, whereas adult stem cells can only form certain types of specialized cells. Stem cells continue to divide as long as the individual remains alive.

**stop codon**: A stop codon is a trinucleotide sequence within a messenger RNA (mRNA) molecule that signals a halt to protein synthesis. The genetic code describes the relationship between the sequence of DNA bases (A, C, G, and T) in a gene and the protein it encodes. The cell reads the sequence of the gene in groups of three bases. Of the 64 possible combinations of three bases, 61 specify an amino acid and 3 are stop codons.

**substitution**: Substitution is a type of mutation where one base pair is replaced by a different base pair. The term also refers to the replacement of one amino acid in a protein with a different amino acid.
susceptibility: Susceptibility is a condition of the body that increases the likelihood that the individual will develop a particular disease. It is influenced by a combination of genetic and environmental factors.

syndrome: A syndrome is a collection of recognizable traits or abnormalities that tend to occur together and are associated with a specific disease.

tandem repeat: A tandem repeat is a sequence of two or more DNA base pairs that is repeated in such a way that the repeats lie adjacent to each other on the chromosome. Tandem repeats are generally associated with noncoding DNA. In some instances, the number of times the DNA sequence is repeated is variable. Such variable tandem repeats are used in DNA fingerprinting procedures.

telomere: A telomere is the end of a chromosome. Telomeres are made of repetitive sequences of noncoding DNA that protect the chromosome from damage. Each time a cell divides, the telomeres become shorter. Eventually, the telomeres become so short that the cell can no longer divide.

thymine: Thymine (T) is one of four chemical bases in DNA, the other three being adenine (A), cytosine (C), and guanine (G). Within the DNA molecule, thymine bases on one strand form chemical bonds with adenine bases on the opposite strand. The sequence of the four DNA bases encodes the cell's genetic instructions.

trait: A trait is a specific characteristic of an organism. Traits can be determined by genes, by the environment, or, more commonly, by interactions between them. The genetic contribution to a trait is called the genotype. The outward expression of the genotype is called the phenotype.

transcription: Transcription is the process of making an RNA copy of a gene sequence. This copy, called a messenger RNA (mRNA) molecule, leaves the cell nucleus and enters the cytoplasm, where it directs the synthesis of the protein it encodes.

transfer RNA (tRNA): Transfer RNA (tRNA) is a small RNA molecule that participates in protein synthesis. Each tRNA molecule has two important areas: a trinucleotide region called the anticodon and a region for attaching a specific amino acid. During translation, each time an amino acid is added to the growing chain, a tRNA molecule forms base pairs with its complementary sequence on the messenger RNA (mRNA) molecule, ensuring that the appropriate amino acid is inserted into the protein.

transgenic: Transgenic means that one or more DNA sequences from another species have been introduced by artificial means. Animals are usually made transgenic by having a small sequence of foreign DNA injected into a fertilized egg or developing embryo. Transgenic plants can be made by introducing foreign DNA into a variety of different tissues.

translation: Translation is the process of translating the sequence of a messenger RNA (mRNA) molecule into a sequence of amino acids during protein synthesis. The genetic code describes the relationship between the sequence of base pairs in a gene and the corresponding amino acid sequence it encodes. In the cell cytoplasm, the ribosome reads the sequence of the mRNA in groups of three bases to assemble the protein.

translocation: Translocation is a type of chromosomal abnormality in which a chromosome breaks and a portion of it reattaches to a different chromosome. Chromosomal translocations can be detected by analyzing karyotypes of the affected cells.
tumor suppressor gene: A tumor suppressor gene directs the production of a protein that is part of the system that regulates cell division. The tumor suppressor protein plays a role in keeping cell division in check. When mutated, a tumor suppressor gene is unable to do its job, and as a result, uncontrolled cell growth may occur. This may contribute to the development of a cancer.

uracil: Uracil (U) is one of four chemical bases that are part of RNA. The other three bases are adenine (A), cytosine (C), and guanine (G). In DNA, the base thymine (T) is used in place of uracil.

vacuole: A vacuole is a membrane-bound cell organelle. In animal cells, vacuoles are generally small and help sequester waste products. In plant cells, vacuoles help maintain water balance. Sometimes a single vacuole can take up most of the interior space of a plant cell.

vector: A vector is any vehicle, often a virus or a plasmid, that ferries a desired DNA sequence into a host cell as part of a molecular cloning procedure. Depending on the purpose of the cloning procedure, the vector may assist in multiplying, isolating, or expressing the foreign DNA insert.

virus: A virus is an infectious agent that occupies a place near the boundary between the living and the nonliving. It is a particle much smaller than a bacterial cell, consisting of a small genome of either DNA or RNA surrounded by a protein coat. Viruses enter host cells and hijack the enzymes and materials of the host cells to make more copies of themselves. Viruses cause a wide variety of diseases in plants and animals, including AIDS, measles, smallpox, and polio.

western blot: Western blotting is a laboratory technique used to detect a specific protein in a blood or tissue sample. The method involves using gel electrophoresis to separate the sample's proteins. The separated proteins are transferred out of the gel to the surface of a membrane. The membrane is exposed to an antibody specific to the target protein. Binding of the antibody is detected using a radioactive or chemical tag. A western blot is sometimes used to diagnose disease.

X chromosome: The X chromosome is one of two sex chromosomes. Humans and most mammals have two sex chromosomes, X and Y. Females have two X chromosomes in their cells, while males have X and Y chromosomes in their cells. Egg cells all contain an X chromosome, while sperm cells contain an X or a Y chromosome. This arrangement means that during fertilization, the male determines the sex of the offspring.

X-linked: X-linked is a trait where a gene is located on the X chromosome. Humans and other mammals have two sex chromosomes, X and Y. In an X-linked or sex-linked disease, it is usually males that are affected because they have a single copy of the X chromosome that carries the mutation. In females, the effect of the mutation may be masked by the second copy of the X chromosome.

Y chromosome: The Y chromosome is one of two sex chromosomes. Humans and other mammals have two sex chromosomes, the X and the Y. Females have two X chromosomes in their cells, while males have X and Y chromosomes in their cells. Egg cells contain an X chromosome, while sperm cells contain an X or a Y chromosome. This arrangement means that during fertilization, the male determines the sex of the offspring.
**Human Genetic Variation**

**yeast artificial chromosome (YAC):** Yeast artificial chromosome (YAC) is a human-engineered DNA molecule used to clone DNA sequences in yeast cells. YACs are often used in connection with the mapping and sequencing of genomes. Segments of an organism's DNA, up to 1 million base pairs long, can be inserted into YACs. The YACs, with their inserted DNA, are then taken up by yeast cells. As the yeast cells grow and divide, they amplify the YAC DNA, which can be isolated and used for DNA mapping and sequencing.

**zebrafish:** The zebrafish is a member of the minnow family. It is a model organism used to study the development of vertebrates because the embryo is transparent, it develops outside its mother, and its development from egg to larva happens in just three days.
Alike, But Not the Same

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 lesson, 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 lesson 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 Lesson 2, in which students consider the significance of human genetic variation at the molecular level.
**Introduction**

This lesson 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 lessons, this concept is less explicit in subsequent lessons than it is in this one.

One goal of the Human Genome Project was to provide the complete sequence of the human genome. Another goal was 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 their 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 lesson, students are introduced to the notion that although we are very similar to one another, we are also very different and our differences reflect a complex interplay between genetic and environmental factors. This understanding sets the stage for subsequent lessons 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.

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**In Advance**

**Web-Based Activities**

None.

**Materials and Preparation**

<table>
<thead>
<tr>
<th>Photocopies and Transparencies</th>
<th>Equipment and Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1 copy of Master 1.1 for each student&lt;br&gt;• 1 copy of Master 1.2 for each student</td>
<td>• plant, fish, prepared slide of bacteria&lt;br&gt;• masking tape for labeled axes on the board or wall in which students can enter data&lt;br&gt;• 120 3 x 5 cards (4 per student; required only if the axes are on the wall)&lt;br&gt;• tape measure (1 per pair of students)</td>
</tr>
</tbody>
</table>

Construct four sets of axes on the board or the classroom wall (use masking tape). Label the axes as shown in Figure 7.
Figure 7. Construct the four sets of axes shown here on the board or on a wall of your classroom.

1. Begin the lesson 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 any one 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 lesson by saying, “Let’s see just how similar you are.” Give 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 it.

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 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 females a different color. This strategy will allow the class to determine whether 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 lesson 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 representing the males.

6. Challenge 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 students to stand.
   - Invite the volunteer to begin to identify his or her phenotype for each of the 13 human traits listed on Master 1.1, *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*.

   **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.

   **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 such variation 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 Lesson 2, *The Meaning of Genetic Variation*.
Human 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 4, page 22). As noted in “Understanding Human Genetic Variation” (pages 19–29), an examination of human proteins demonstrated that about 85 percent of all variation occurred within populations, whereas only 15 percent occurred between populations. That is, we are more “like” people with other ethnic or geographic origins than we might think.

9. Invite students to summarize the lesson’s major concepts by asking, “What has this lesson 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 may also 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 Lesson 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 lessons in this module.
This lesson 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 biological parents).
**Lesson 1 Organizer**

<table>
<thead>
<tr>
<th>What the Teacher Does</th>
<th>Procedure Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tell the class something like this: “If a visitor from another planet walked into this classroom, he might easily conclude that humans all look very much alike.” Ask, “Do you agree with this statement?” Use examples to help students recognize that humans are more similar to each other than they are to other species and that humans have a set of traits that define us as a species.</td>
<td>Page 65 Step 1</td>
</tr>
<tr>
<td>Invite students to explore similarities among classmates. Give each student one copy of Master 1.1 and ask them to work in pairs to complete it. Define terms (on page 65) if unfamiliar to students.</td>
<td>Page 65 Step 2</td>
</tr>
<tr>
<td>Ask students to enter data from their copy of Master 1.1 onto graphs you prepared on the board.</td>
<td>Page 66 Step 3</td>
</tr>
<tr>
<td>Have class analyze data on graphs and identify evidence that supports the idea that students share many traits with other class members.</td>
<td>Page 66 Step 4</td>
</tr>
<tr>
<td>Continue by pointing out that you can see that individuals are different. Ask students, “What evidence supports that people are different?”</td>
<td>Page 66 Step 5</td>
</tr>
<tr>
<td>Ask students how many traits they would need to consider to identify a given student as unique. Write predictions on the board.</td>
<td>Page 66 Step 6</td>
</tr>
<tr>
<td>Conduct the game described in Step 7 to determine uniqueness among class members.</td>
<td>Page 67 Step 7</td>
</tr>
<tr>
<td>Give each student a copy of Master 1.2. Ask students to work in pairs to answer the questions. Discuss answers with the class (on pages 67 to 68).</td>
<td>Page 67 Step 8</td>
</tr>
<tr>
<td>Ask, “What has this lesson illustrated about how one human compares with another human? What has it illustrated about human variation in general?” Ask students to summarize their ideas and share with the class.</td>
<td>Page 68 Step 9</td>
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</tbody>
</table>

M = Involves copying a master.
The Meaning of Genetic Variation

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

**Major Concept**
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 lesson, 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 appear to 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 lesson 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
Human Genetic Variation

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 lesson.

Introduction

As discussed in Understanding Human Genetic Variation (pages 19–29), there is considerable variation between the genomes of any two individuals, but only a small amount of that variation appears to have any significant biological impact, that is, produces differences in function. The Human Genome Project, completed in 2003, illuminated the extent of human genetic variation as well as the variations that have biological significance.

This lesson 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.

In Advance

Web-Based Activities

Day 1, Step 12.

Day 2, Step 4.

Materials and Preparation

<table>
<thead>
<tr>
<th>Photocopies and Transparencies</th>
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<tr>
<td>• 1 copy of Master 2.1 for each student</td>
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<td></td>
</tr>
<tr>
<td>• 1 copy of Master 2.4 for each student</td>
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</tr>
<tr>
<td>• 1 copy of Master 2.5 for each student*</td>
<td></td>
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<tr>
<td>• 1 copy of Master 2.6 for each group</td>
<td></td>
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<tr>
<td>• (Optional) Computers with Internet access</td>
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</table>

*Needed only by classes without Internet access.

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 you’d need is on page 77.

Follow the instructions on page 77 to get to the Web site students will use to view the video documentary (Step 12). If you do not have Internet access, you can use the print-based alternative (also discussed on page 77).
DAY 1

1. Introduce the lesson by asking students to identify the ultimate source of the variation they investigated in Lesson 1.

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

2. Explain that in this lesson, students will investigate human genetic variation at the molecular level and examine the impact of that variation on biological function. Give one copy of Master 2.1, How Much Variation? Beta Globin Gene—Person A, and Master 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 in Masters 2.1 and 2.2. Explain that geneticists use shortcuts 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 encode a protein; the entire gene has only about 1,700 nucleotide pairs and includes just two introns. The sequences on Masters 2.1 and 2.2 do not show the gene’s promoter regions but begin with the first sequences that are translated.

3. Ask students to read the paragraph at the top of each page and then estimate the total number of bases on each page. Direct students to write their estimate in the space provided on the masters.

   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 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 should also 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 about 3 billion bases long. Ask the students how they might use the sequences from 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 the two people 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. Give 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 $2/1,691 = 0.001$ (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 $0.001 \times 100 = 0.1$ percent.

The total number of base differences would be $3,000,000,000 \times 0.001 = 3,000,000$ or, in scientific notation, $3 \times 10^6$. 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 is likely 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 chromosomes), 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 should also 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 lesson 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 Lesson 1 and point out that most of these differences have their basis in a difference in the DNA sequence of particular genes (pierced versus nonpierced body parts probably do not). To help them understand the magnitude of the number of differences between their DNA and that of another person, ask students whether they think there are 3 million differences in appearance and biological functions between themselves and the person sitting next to them (discussed in Step 10, below).

9. Explain that studying the beta globin gene more closely will help students begin to answer these questions for themselves. Have students examine the sequences on Master 2.1, Beta Globin Gene—Person A, and Master 2.2, 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.

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.

Note: 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 them. 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.

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.

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 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, 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. **Step 12 for classes with access to the Internet:** Tell students that in the next part of the lesson, they will consider the consequences of the genetic variation that results in sickle cell disease. Hand out Master 2.4, *Exploring Sickle Cell Disease*, and direct students to organize into small groups. Have students view the documentary “What Is Sickle Cell Disease?” on the student section of the Human Genetic Variation Web site (http://science.education.nih.gov/supplements/genetic/student; click on “The Meaning of Genetic Variation”) and begin working on the questions.

13. When students reach Question 2 on Master 2.4, they should explain how they intend to test the Lindsey twins. Give the group a copy of the test results (Master 2.6, *Results of the Lindsey Test*) after the students correctly explain the test they would have conducted.

**Optional alternative to Master 2.6:** Instead of giving students the results of the test they propose in Question 2 on Master 2.4, you may want them to complete the relevant laboratory activity themselves. Kits are available that you can adapt to this purpose. Some use proteins that represent hemoglobin from normal, sickle cell, and sickle cell trait (heterozygous) individuals. The test results on Master 2.6 are based on DNA from such individuals. If you use a kit, be sure to make this distinction clear to students. If you plan to have your students complete the lab, schedule an additional half to whole class period for the activity.
DAY 2

1. Open the second half of the lesson by directing students to meet in their groups to complete or review their answers to the questions on Master 2.4, Exploring Sickle Cell Disease. After they have completed their work, convene a class discussion in which students can 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 Hb A?

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.

**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 DNA from Jason and from Sondra and treat it for analysis of alleles of the beta globin gene. Use gel electrophoresis to visualize the alleles present in each twin’s DNA. “Standards,” or controls, of DNA from people with the normal (Hb A) and sickle (Hb S) alleles should be included for comparison. (Unless you have previously discussed restriction enzymes and RFLP analysis, you probably do not want to introduce these concepts here. Instead, just explain to students that DNA isolated from individuals can be treated in ways that make different alleles show different gel electrophoresis patterns.)

If a twin has normal hemoglobin, his or her DNA will migrate on the gel in the same pattern as the DNA standard for the Hb A allele. If a twin has sickle cell disease, his or her hemoglobin will migrate in the pattern of the DNA standard for the Hb S allele. If a twin is heterozygous (has sickle cell trait), his or her DNA will contain two different alleles for the hemoglobin gene and show both the pattern of the Hb A standard and the pattern of the Hb S standard.

Some students may suggest an alternative procedure that uses gel electrophoresis with hemoglobin proteins from the twins’ blood to reveal their genotypes. Hb A and Hb S migrate differently in an electrical field because of differences in their electrical charges. Master 2.6, Results of the Lindsey Test, however, shows the results for the DNA test for different alleles of the beta globin gene because this module focuses on DNA. If students propose a test for the Hb A and Hb S proteins, ask them to think about what the different proteins imply about the genes for those proteins. Then, ask them to devise a DNA-based test instead.

**Question 3. Write the dialogue for a brief scene (2 to 3 minutes) 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 had sickle cell trait; that is, they are both heterozygous for the sickle cell allele and the normal allele, because neither of them are or 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.
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 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 is also positive?”

Entertain several answers to this question.

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

4. Step 4 for classes with access to the Internet: 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 Web site 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. Go to http://science.education.nih.gov/supplements/genetic/student and click on “The Meaning of Genetic Variation” to access the database.

Step 4 for classes without access to the Internet: Ask students, as a final challenge, to imagine that they are doctors practicing in Cameroon, in west-central Africa. Direct them to return to Master 2.5, Reference Database: Sickle Cell Disease 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 0.25 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 was 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 lesson 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 Hb A?

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 (Hb A/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.

- 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, or 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 is also 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.
### Lesson 2 Organizer: WEB VERSION

#### Day 1

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<td>Ask students to identify the source of the variation they observed in Lesson 1.</td>
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<tr>
<td>Explain that students will investigate human genetic variation at the molecular level and examine the impact of variation on biological function. Give each student one copy of Masters 2.1 and 2.2. Explain that the sequences come from the beta globin gene from two different people.</td>
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<td>Ask students to read the top paragraph on each master, estimate the number of bases on each, and write their estimates on the masters.</td>
<td>Page 73 Step 3</td>
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<td>Ask students what they notice when they compare the sequence from person A with the sequence from person B.</td>
<td>Page 74 Step 4</td>
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<tr>
<td>Point out that this sequence is 1,691 bases long and the complete human genome is about 3 billion bases. Ask students how they might use the sequences from person A and person B and the total size of the human genome to estimate the extent of variation between the two people. Ask what assumptions they would make to estimate the variation.</td>
<td>Page 74 Step 5</td>
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<tr>
<td>Give each student one copy of Master 2.3. Direct students to use this handout as a guide to estimating variation.</td>
<td>Page 74 Step 6 M</td>
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<td>Ask students what their estimates indicate about the extent of human variation at the molecular level.</td>
<td>Page 75 Step 7</td>
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<tr>
<td>Explain that the rest of the lesson focuses on this 0.1 percent difference between people. Ask 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?”</td>
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<tr>
<td>Tell students that studying the beta globin gene more closely will help them answer these questions. Have students examine the sequences on Masters 2.1 and 2.2 again. Explain that the bases grouped in triplets are from the coding regions (exons) of the gene while other regions are noncoding (introns). Then ask, “Which of the differences in bold is most likely to matter, and why?”</td>
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<td>Explain that although 3 million bases sounds like a lot, most differences have no significant impact because they occur in a noncoding region or have no known function. Point out that most of the 3 million differences can be detected only by examining the DNA sequence.</td>
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<tr>
<td>Tell students that they will next consider the consequences of the genetic variation that results in sickle cell disease. Give each student a copy of <strong>Master 2.4</strong>. Direct students to form small groups to watch the online documentary “What Is Sickle Cell Disease?” and begin working on the questions. After groups have proposed a procedure for Question 2 on <strong>Master 2.4</strong>, give each group a copy of the test results, <strong>Master 2.6</strong>.</td>
<td>Page 77 Steps 12, 13</td>
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<tr>
<td><strong>Optional alternative to Master 2.6:</strong> Have students do the lab activity themselves.</td>
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<td>Direct groups to complete or review answers to questions on <strong>Master 2.4</strong>. Convene a class discussion in which students can share their answers.</td>
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<td>Ask students what the beta globin gene and sickle cell disease illustrate about human genetic variation.</td>
<td>Page 80 Steps 2</td>
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<td>Summarize 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?” Allow several students to respond.</td>
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<td>Challenge students to imagine they are doctors practicing in Cameroon in west-central Africa. Have students use the resources on the Web site to compare the incidence of sickle cell disease in Cameroon with the incidence in the United States and to determine how scientists explain the difference.</td>
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<td>Ask students how this information would change what they would say to Ms. Lindsey.</td>
<td>Page 81 Steps 5</td>
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<tr>
<td>Close the lesson by asking students the following questions: • “Will natural selection favor the survival of people who produce Hb S or people who produce Hb A?” • “All populations have genetic variations that lead to increased incidence of particular disorders. Why would such apparently harmful variations have been maintained in those populations?”</td>
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= Involves copying a master.

= Involves using the Internet.
# Lesson 2 Organizer: PRINT VERSION

## Day 1

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  - “What effect do you think they have?”  
  - “What might affect how much a specific difference matters?” | Page 75 Step 8      |
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**Point out the codon in which the first difference occurs.** Tell students that person A has normal hemoglobin, while person B has abnormal hemoglobin associated with sickle cell disease. Explain that the single base difference in this codon determines whether the person has normal or sickle hemoglobin.

Tell students that they will next consider the consequences of the genetic variation that results in sickle cell disease. Give each student one copy of Masters 2.4 and 2.5. Direct students to organize into small groups and to begin working on the questions. After groups have proposed a procedure for Question 2 on Master 2.4, give each group a copy of the test results, Master 2.6.

**Optional alternative to Master 2.6:** Have students do the lab activity themselves.

#### Day 2

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**What the Teacher Does**

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Direct groups to complete or review answers to questions on Master 2.4. Convene a class discussion in which students can share their answers.

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

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Challenge students to imagine they are doctors practicing in Cameroon in west-central Africa. Have students use the Reference Database (Master 2.5) to compare the incidence of sickle cell disease in Cameroon with the incidence in the United States and to determine how scientists explain the difference.

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Close the lesson by asking students the following questions:
- Will natural selection favor the survival of people who produce Hb S or people who produce Hb A?
- All populations have genetic variations that lead to increased incidence of particular disorders. Why would such apparently harmful variations have been maintained in those populations?

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**I** = For classes without access to the Internet.
Molecular Medicine Comes of Age

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 lesson, students will
- appreciate that identifying and sequencing disease-related genes helps scientists better understand and treat disease;
- be able to explain that in the future, physicians will change how they prescribe drugs because of our increasing understanding of how genetic differences among people affect response to drug treatment;
- 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 will likely 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 lesson 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 has been significantly changing not only how we think about human disease, but how we treat it.
Lessons 3 and 4 focus students’ attention on the practical, medical applications of understanding human genetic variation at a molecular level.

Lesson 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, Lesson 3 focuses on those portions of Figure 6 (on page 25) that deal with pharmacogenomics and targeted drug therapy. An extension to Lesson 3 invites students to consider gene therapy as another strategy made possible by knowledge of molecular genetics.

Geneticists have long 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, people 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 April 15, 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 have also 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 about 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. A recent article by scientists from the National Human Genome Research Institute is an excellent review of the history and current state of genomic medicine (Green et al., 2011).
In this lesson, students assume the roles of employees of two fictional pharmaceutical companies, Firm A and Firm B. Each company 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. Students 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 of the ways 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 both pharmacogenomics and targeted drug therapy are still in their early stages, this lesson 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—is already upon us. Although molecular medicine is just beginning to develop, the field has enormous potential for the improvement of personal and public health.

**Web-Based Activities**
Steps 4 and 6.

**Materials and Preparation**

<table>
<thead>
<tr>
<th>Photocopies and Transparencies</th>
<th>Equipment and Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1 transparency of Master 3.1</td>
<td>• (Optional) Computers</td>
</tr>
<tr>
<td>• 1 copy of Masters 3.2–3.5 for each group that will complete this part of the lesson (Firm A)</td>
<td>with Internet access</td>
</tr>
<tr>
<td>• 1 transparency and 1 copy of Master 3.6 for each student who will complete this part of the lesson</td>
<td></td>
</tr>
<tr>
<td>• 1 copy of Master 3.7 for each Firm A group</td>
<td></td>
</tr>
<tr>
<td>• 1 copy of Masters 3.8–3.11 for each group that will complete this part of the lesson (Firm B)</td>
<td></td>
</tr>
<tr>
<td>• 1 transparency and 1 copy of Master 3.12 for each student who will complete this part of the lesson</td>
<td></td>
</tr>
<tr>
<td>• 1 copy of Master 3.13 for each Firm B group</td>
<td></td>
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</tbody>
</table>
1. Introduce the lesson by displaying a transparency of Master 3.1, *Molecular Medicine Comes of Age*, and asking students what they think the statement means and whether they can think of any examples that illustrate or provide evidence for this statement.

   Students should be able to explain that understanding human genetic variation at a molecular level means identifying the specific differences in the base sequence that distinguish one human from another. Although students will likely not mention pharmacogenomics and targeted drug therapy as examples of healthcare 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 that finding and sequencing the gene related to a disease could help scientists develop ways to treat it?”

2. Explain that the students’ challenge in this lesson is to investigate two examples that illustrate and provide evidence for this statement. Explain further that students will investigate these examples by acting as groups of employees in two pharmaceutical companies facing problems that threaten the companies’ futures.

3. Divide the class in half and explain that one-half will act as employees in Firm A and the other half, 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 groups of four. Give one copy each of Masters 3.2, 3.3, 3.4, and 3.5, *Saving Firm A, [Role]*, to each group 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 group in the other half. Also give 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 students should use these forms to organize their discussions and report the results of their work.

   For an introduction to the different roles for Firm A, students can view the Lesson 3 videos on the Human Genetic Variation Web site. Go to [http://science.education.nih.gov/supplements/genetic/student](http://science.education.nih.gov/supplements/genetic/student) and click on “Molecular Medicine Comes of Age” to access the videos.

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

   Master 3.5, *Saving Firm A, Role: Biostatistician*, involves somewhat more challenging analysis than the other roles. You may want to consider assigning students who have stronger mathematical analysis skills to the biostatistician role.
6. Give the groups 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. They should use the Report Form (Master 3.6 or 3.12) to organize their thoughts.

When students reach Step 6 on Master 3.6 or Step 5 on Master 3.12, they will ask you, as vice president of the company, for additional data (Master 3.7, Some New Genetic Data about Firm A, or Master 3.13, Some New Information about Firm B). You can give the groups copies of the masters, or you can devise an approach that requires students to search for the data.

Students can also go to the Human Genetic Variation Web site and view the video “New Data” when they reach Step 6. Go to http://science.education.nih.gov/supplements/genetic/student and click on “Molecular Medicine Comes of Age” to access New Data. Access to the video is password protected. Give students the password: gene.

7. After 30 minutes, 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 groups’ work.

8. Display a transparency of Master 3.6, Report Form for Firm A, and use it to guide the discussion by asking groups from Firm A to present their answers to the questions (a different group should answer each question). After one group 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?

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

**Question 2.** Describe asthma in your own words (refer to Master 3.2, Saving Firm A, Role: Team Coordinator, and Master 3.3, Saving Firm A, Role: Physiologist).

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

**Question 3.** What is Drug X designed to do for asthma sufferers (refer to Master 3.2, Saving Firm A, Role: Team Coordinator, and Master 3.3, Saving Firm A, Role: Physiologist)?

The drug opens up the bronchioles to make breathing easier.

An interesting way to assess students’ understanding of this information is to ask one group to offer an answer to a question and a different group 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 group members who provide the initial answer.

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**Student Lesson 3**
Question 4. Look at the preliminary test results (refer to Master 3.5, Saving Firm A, Role: Biostatistician). 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.

No to all three questions. Students should recognize that the proportion of children who experience relief from the symptoms of asthma is the same for males and females and for children who do and do not own pets. In all cases, about one-third experience significant relief, slightly more than 40 percent experience some relief, and nearly one-fourth experience no relief. The constancy of these proportions means that 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 Master 3.4, Saving Firm A, Role: Molecular Biologist) 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’s genotype to determine whether Drug X will be effective with that individual.

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

The group’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 healthcare professionals so they understand the test and the results and can explain this information to their patients?
9. Repeat the same process with the groups 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 Master 3.8, Saving Firm B, Role: Team Coordinator)?**

Drug Y is a successful treatment for cystic fibrosis (CF) and 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 Master 3.9, Saving Firm B, Role: Physiologist).**

CF is a genetic disease that causes the body to produce 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 Master 3.10, Saving Firm B, Role: Molecular Biologist)?**

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 into and out of the cell and the 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 Master 3.11, Saving Firm B, Role: Physician, 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 Master 3.11.
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 approach is different from 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 Master 3.10. 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 group solved the problem facing the company with respect to Drug Y? What new problems has it raised?

No, the group 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 group’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 Food and Drug Administration (FDA) approval for the new treatment.
10. Challenge 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 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 intended for people who have certain genotypes. They may also 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 (page 25) 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.

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

11. Display again the transparency you made from Master 3.1, *Molecular Medicine Comes of Age*. Ask students to explain what it means, and provide examples that illustrate or serve as evidence for this point.

12. Close the lesson by asking students what they think the transparency’s title means.
### Lesson 3 Organizer

<table>
<thead>
<tr>
<th>What the Teacher Does</th>
<th>Procedure Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Display a transparency of <strong>Master 3.1</strong>. Ask students what they think the statement means and whether they can think of examples that illustrate or provide evidence for this statement.</td>
<td>Page 90 Step 1</td>
</tr>
<tr>
<td>Explain that to investigate this statement, students will work in groups as employees of two pharmaceutical companies that are facing problems.</td>
<td>Page 90 Step 2</td>
</tr>
<tr>
<td>Have one-half the class act as employees in Firm A and the other half, in Firm B. Tell students that the two companies face different problems, but both problems can be solved in ways that relate to the statement on the transparency.</td>
<td>Page 90 Step 3</td>
</tr>
<tr>
<td>Direct students to work in groups of four. Give each group that will work as Firm A a copy of <strong>Masters 3.2, 3.3, 3.4, and 3.5</strong>. Give each group that will work as Firm B one copy of <strong>Masters 3.8, 3.9, 3.10, and 3.11</strong>. Give each student a copy of either <strong>Master 3.6</strong> (Firm A) or <strong>Master 3.12</strong> (Firm B) and explain that these forms will help them organize their discussions and report their results.</td>
<td>Page 90 Step 4*</td>
</tr>
<tr>
<td>Instruct groups to decide who will play each of the four roles and to distribute the masters accordingly.</td>
<td>Page 90 Step 5</td>
</tr>
<tr>
<td>Allow 30 minutes for groups to complete their reports on Master 3.6 or 3.12. When students ask for additional data, give them <strong>Master 3.7</strong> or <strong>3.13</strong>. At the end of that time, groups should be ready to defend their analysis and to present their suggested solution to the class.</td>
<td>Page 91 Step 6*</td>
</tr>
<tr>
<td>Call the class to order. Explain that you will assume the role of vice president for research first for Firm A and then for Firm B.</td>
<td>Page 91 Step 7</td>
</tr>
<tr>
<td>Display a transparency of <strong>Master 3.6</strong>. Use it to guide the discussion about Firm A. After Firm A groups share their ideas, ask if other class members have questions or comments.</td>
<td>Page 91 Step 8</td>
</tr>
<tr>
<td>Display a transparency of <strong>Master 3.12</strong>. As before, use it to guide the discussion about Firm B.</td>
<td>Page 93 Step 9</td>
</tr>
<tr>
<td>Challenge students to use these questions to generalize what they learned: • How is genetic variation related to the use of drugs? • How will pharmaceutical companies likely use our increasing understanding of human genetic variation? • How can discovering the genes associated with genetic disorders help scientists develop new approaches to treatment?</td>
<td>Page 95 Step 10</td>
</tr>
<tr>
<td>Display again the transparency of <strong>Master 3.1</strong>. Ask students to explain the statement and provide examples.</td>
<td>Page 95 Step 11</td>
</tr>
<tr>
<td>Close the lesson by asking students what they think the title on the transparency of <strong>Master 3.1</strong> means.</td>
<td>Page 95 Step 12</td>
</tr>
</tbody>
</table>

**= Involves copying a master.  
*T= Involves making a transparency.  
* = Involves optional online video vignette.
Are You Susceptible?

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 better diagnosis, prevention, and treatment.

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

For the most part, the treatment of genetics in high school focuses on single-gene traits. In addition, most of the single-gene traits discussed 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 behavioral characteristics that are controversial and that often attract media attention—for example, intelligence, sexual preference, aggression, and 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 disorder (manic-depressive illness). Research has already 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, probably 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 diseases will introduce some new challenges for the public, chief among them the notions of susceptibility and risk. You may learn from a “positive” test that you are susceptible to developing the disease in question, but that will not mean that you are destined to develop the disease. Nor will a “negative” test mean that you definitely will not develop the disease. In addition, while you 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 diseases through a combination of medication and environmental modification. That, of course, requires a partnership between patients and healthcare providers to identify and modify the environmental variables that magnify one’s genetic risks. That is the ultimate message of this lesson.

**Web-Based Activities**

None.

**Materials and Preparation**

<table>
<thead>
<tr>
<th>Photocopies and Transparencies</th>
<th>Equipment and Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1 copy of Master 4.1 for each student</td>
<td></td>
</tr>
<tr>
<td>• 1 copy of Master 4.2 for each student</td>
<td></td>
</tr>
<tr>
<td>• Copies of Masters 4.3–4.6, cut up and put into envelopes</td>
<td></td>
</tr>
<tr>
<td>• Dice (1 die per group of 3 students)</td>
<td></td>
</tr>
<tr>
<td>• Relevant-genes envelopes (1 envelope per student)</td>
<td></td>
</tr>
</tbody>
</table>

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."
Human Genetic Variation

**Procedure**

1. Begin the lesson by asking students to suggest definitions of the term “risk.” You might prompt the discussion by asking students to think about risky behaviors that are a part of adolescence. Write three or four of the 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 a heart attack or of getting 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?


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 supply the heart, a heart attack can result. Ask 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
concentrations in the blood, or 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 might thus
reduce the risk of premature heart attack for a person who carries the
*PL(A2)* mutation.

6. Explain 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 buildup of cholesterol deposits in the
arteries. In this lesson, 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. Give each student one copy of Master 4.1, *Rolling the Dice*, and direct
students to work in groups 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 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 ones. 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. Give each student one relevant-genes envelope and explain that this envelope contains information about his or her genetic risk for a fatal heart attack. Ask 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. Give one copy of Master 4.2, Thinking About the Game, to each student, and ask students to complete the master to compare the results of the game with and without considering genetic factors.

13. Conclude the lesson by inviting each group to offer its answer to one of the questions on Master 4.2. Then, invite other groups to contribute additional insights or information or to challenge ideas expressed by other groups.

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 usually 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 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 by modifying risky behaviors.

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

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

If we know that we are at increased genetic risk for a particular disease, we can try to avoid environmental factors, such as risky behaviors, that increase the risk further. Many healthcare professionals think that increased understanding of genetic variation will provide an important impetus to preventive medicine. Prevention will require a close partnership between healthcare providers and consumers. Healthcare 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) is generally a rather passive recipient of health care.
## Lesson 4 Organizer

<table>
<thead>
<tr>
<th>What the Teacher Does</th>
<th>Procedure Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask students to suggest definitions for the term “risk.” Ask students to think about risky behaviors that are part of adolescence. Write several definitions on the board.</td>
<td>Page 100 Step 1</td>
</tr>
<tr>
<td>Ask students whether they think risks can be modified.</td>
<td>Page 100 Step 2</td>
</tr>
<tr>
<td>Read aloud the story on page 100, “Death of an Olympic Champion.”</td>
<td>Page 100 Step 3</td>
</tr>
<tr>
<td>Explain that 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 supply the heart, a heart attack can result. Ask students to consider whether this mutant allele influenced Grinkov’s risk of a heart attack.</td>
<td>Page 100 Step 4</td>
</tr>
<tr>
<td>Ask the class to suggest ways that Grinkov could have modified his behavior if he had known he was at increased risk for premature heart attack.</td>
<td>Page 101 Step 5</td>
</tr>
<tr>
<td>Explain 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. Tell students that they will now explore medical risk and learn how genetic analysis is helping us understand and define risk in new ways.</td>
<td>Page 101 Step 6</td>
</tr>
<tr>
<td>Give each student a copy of Master 4.1. Have students work in groups of three to play the game.</td>
<td>Page 101 Step 7</td>
</tr>
<tr>
<td>Ask how many students suffered a fatal heart attack. Record on the board the life stages at which the heart attacks occurred.</td>
<td>Page 101 Step 8</td>
</tr>
<tr>
<td>Ask students how the game is and is not like real life.</td>
<td>Page 101 Step 9</td>
</tr>
<tr>
<td>Acknowledge the importance of genetic risk factors in the development of heart disease. Ask students how factoring this information into the game could affect the outcome.</td>
<td>Page 102 Step 10</td>
</tr>
<tr>
<td>Give one relevant-genes envelope to each student, and explain that it contains information about their genetic risk for a fatal heart attack. Ask students to open the envelopes and share their heart points until you have addressed all four values: $-10$, 0, $+10$, and $+40$. Point out that genetic risk falls off rapidly as genetic relatedness decreases. Explain that this is the case generally for multifactorial diseases.</td>
<td>Page 102 Step 11</td>
</tr>
</tbody>
</table>
**Human Genetic Variation**

<table>
<thead>
<tr>
<th>What the Teacher Does</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Give each student a copy of Master 4.2. Ask students to complete the master to compare the results of the game with and without considering genetic factors.</td>
<td>Page 102</td>
</tr>
<tr>
<td>Conclude the lesson by asking groups to answer one of the questions on Master 4.2. Invite other groups to contribute additional thoughts or challenge ideas.</td>
<td>Page 102</td>
</tr>
</tbody>
</table>

*M* = Involves copying a master.
LESSON 5
Evaluate

Making Decisions in the Face of Uncertainty

Focus
Students analyze a 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 lesson, 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 should also 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
Human Genetic Variation

breast cancer that this lesson 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 lesson 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 lesson 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. Groups 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 people 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 lesson'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 is already 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 genetic variation that exists among humans. Our understanding of genetic factors that can predispose individuals to certain cancers, while increasing, is still 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.
**Web-Based Activities**
Steps 2 and 3.

**Materials and Preparation**

<table>
<thead>
<tr>
<th>Photocopies and Transparencies</th>
<th>Equipment and Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Make 1 copy of Master 5.1 for each student*</td>
<td>• (Optional) Computers with Internet access</td>
</tr>
<tr>
<td>• Make 1 copy of Master 5.2 for each student</td>
<td></td>
</tr>
<tr>
<td>• Make 1 copy of Master 5.3 for each student*</td>
<td></td>
</tr>
</tbody>
</table>

*Needed only by classes without access to the Internet.

Follow the instructions on page 110 to get to the Web site on the computers students will use. If you do not have enough computers with Internet access, you can use the print-based alternative (on pages 110 and 111).

**Tips from the field test**

Teachers who tested this lesson 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.

**Procedure**

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

   With approximately one in eight 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 lesson, and unusual silence or reticence) and provide appropriate support.**
Steps 2 and 3 for classes with access to the Internet:

2. Direct students to organize into their small groups and watch the five online videos under “Making Decisions in the Face of Uncertainty” (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. Go to http://science.education.nih.gov/supplement/genetic/student and click on “Making Decisions in the Face of Uncertainty” to access the videos.

3. Give each student one copy of Master 5.2, Analyzing the Issues, 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 Master 5.2. Discuss each segment in turn, as students complete it, using the questions on Master 5.2 as a guide. Address any other questions the students raise as well.

Steps 2 and 3 for classes without access to the Internet:

2. Give each student one copy of Master 5.1, Making Decisions in the Face of Uncertainty. Direct students to organize into their small groups and to select students to read the parts of the various characters. Ask students simply to read the script all the way through so they can get a sense of the complete case.

3. Give each student one copy of Master 5.2, Analyzing the Issues, and one copy of Master 5.3, Reference Database, and explain that now the class will read the script again, one segment at a time. Suggest that students take notes and list questions that occur to them as they read each segment, then respond to the related questions on Master 5.2. Discuss each segment in turn, as students complete it, using the questions on Master 5.2 as a guide. Address any other questions the students raise as well.

If students raise questions about the science, legal, or 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 2010, when this module was reprinted, the laboratory cost for the combined test for BRCA1 and BRCA2 ranged from several hundred to several thousand dollars. There would be additional
costs for the associated genetic counseling. Insurance coverage varies depending on the company.

**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 partner (if she has one).

**Question 3. What arguments support having the test?**

This is a good opportunity to ensure that the students understand the underlying science in this case study.

For classes with access to the Internet:
Files in the online Breast Cancer Database will help students learn about the science. Go to [http://science.education.nih.gov/supplement/genetic/student](http://science.education.nih.gov/supplement/genetic/student) and click on “Making Decisions in the Face of Uncertainty” to access the database. Students can access those files on their own, if you have enough computers with access to the Internet.

For classes without access to the Internet:
Information in Master 5.3, Reference Database, will help students learn about the science.

Beth will no longer 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 hereditary. The form of cancer that Beth's mother has may not be hereditary. 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 healthcare provider to conduct a genetic test is based on a variety of factors. Healthcare 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 healthcare 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 healthcare 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 healthcare 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 healthcare 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 90 percent. Some recent data suggest a risk figure even lower than 60 percent. In fact, as is often true when a new medical test becomes available, the exact figure is still unknown. Further, it appears that the risk figure may vary, depending upon the particular mutation in the BRCA1 gene that an individual woman carries.

Students have also 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 lesson 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 groups to discuss these questions. Then, use the following questions to stimulate a brief, final class discussion about the lesson.

- Our understanding of and ability to identify genetic differences among us has increased remarkably in the past 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 most likely would have undergone a radical mastectomy if cancer was discovered. Our increased knowledge of human genetic variation

Use students’ answers to these questions to assess their understanding of the lesson’s major concepts.
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 are already 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.

- How does this lesson 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 lesson 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 choose 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 lesson by challenging students to connect what they learned in Lesson 5 with what they learned in the two preceding lessons. For example, ask students to connect Lesson 5 with Lesson 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 “Mapping the Cancer Genome,” by F.S. Collins and A.D. Barker, in the March 2007 Scientific American, or “Making Headway Against Cancer,” by J. Rennie and R. Rusting, in the September 1996 special edition of Scientific American.

Likewise, connect Lesson 5 with Lesson 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 healthcare choices.
Lesson 5 Organizer: WEB VERSION

<table>
<thead>
<tr>
<th>What the Teacher Does</th>
<th>Procedure Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask students if they know anyone who has had breast cancer. Invite students who wish to briefly describe their relationship to the individual involved to do that.</td>
<td>Page 109 Step 1</td>
</tr>
<tr>
<td>Tell students to organize into their small groups. Have students watch the online videos in “Making Decisions in the Face of Uncertainty.”</td>
<td>Page 110 Step 2</td>
</tr>
<tr>
<td>Give each student one copy of <strong>Master 5.2</strong>. Explain that they will watch the videos again, one segment at a time. Suggest that students take notes and list questions that arise.</td>
<td>Page 110 Step 3 M</td>
</tr>
<tr>
<td>Ask students to respond to the questions on <strong>Master 5.2</strong> after they watch each segment. Discuss each segment, their answers to the questions, and any other questions students have.</td>
<td>Page 110 Step 3</td>
</tr>
</tbody>
</table>
| Challenge students to identify the questions that now face Jennifer about her own health and personal welfare. Invite neighboring groups to discuss the questions. Use the following questions to stimulate a final class discussion:  
  • 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?  
  • How does this lesson illustrate the old saying that knowledge plus choice equals power? | Page 115 Step 4     |

**M** = Involves copying a master.  
**WWW** = Involves using the Internet.
## Lesson 5 Organizer: PRINT VERSION

<table>
<thead>
<tr>
<th>What the Teacher Does</th>
<th>Procedure Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask students if they know anyone who has had breast cancer. Invite students who wish to briefly describe their relationship to the person to do so.</td>
<td>Page 109 Step 1</td>
</tr>
<tr>
<td>Give each student one copy of Master 5.1. Direct students to work in small groups and to select students to read the parts of the various characters. Ask students to then read the script all the way through.</td>
<td>Page 110 Step 2 M</td>
</tr>
<tr>
<td>Give each student one copy of Masters 5.2 and 5.3. Explain that the class will read the script again, one segment at a time. Suggest that students take notes and list questions that arise.</td>
<td>Page 110 Step 3 M</td>
</tr>
<tr>
<td>Ask students to respond to the questions after they read each segment. Discuss each segment, their answers to the questions on Master 5.2, and any other questions that students have.</td>
<td>Page 110 Step 3</td>
</tr>
<tr>
<td>Challenge students to identify the questions that now face Jennifer about her own health and personal welfare. Invite neighboring groups to discuss the questions. Use the following questions to stimulate a final class discussion: • 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? • How does this lesson illustrate the old saying that knowledge plus choice equals power?</td>
<td>Page 115 Step 4</td>
</tr>
</tbody>
</table>

M = Involves copying a master.

= For classes without access to the Internet.
Masters

Lesson 1, Alike, But Not the Same
Master 1.1, An Inventory of a Few Human Traits .......................... student copies
Master 1.2, Thinking About Human Variation ............................... student copies

Lesson 2, The Meaning of Genetic Variation
Master 2.1, How Much Variation? Beta Globin Gene—Person A ........ student copies
Master 2.2, How Much Variation? Beta Globin Gene—Person B ........ student copies
Master 2.3, How Much Variation? Doing the Math .......................... student copies
Master 2.4, Exploring Sickle Cell Disease ................................. student copies (print version only)
Master 2.5, Reference Database: Sickle Cell Disease ................... student copies (print version only)
Master 2.6, Results of the Lindsey Test ................................. group copies

Lesson 3, Molecular Medicine Comes of Age
Master 3.1, Molecular Medicine Comes of Age .......................... transparency
Master 3.2, Saving Firm A, Role: Team Coordinator .................. group copies
Master 3.3, Saving Firm A, Role: Physiologist .......................... group copies
Master 3.4, Saving Firm A, Role: Molecular Biologist ................. group copies
Master 3.5, Saving Firm A, Role: Biostatistician ......................... group copies
Master 3.6, Report Form for Firm A .................................. student copies and transparency
Master 3.7, Some New Genetic Data about Firm A .................. group copies
Master 3.8, Saving Firm B, Role: Team Coordinator .................. group copies
Master 3.9, Saving Firm B, Role: Physiologist .......................... group copies
Master 3.10, Saving Firm B, Role: Molecular Biologist ............... group copies
Master 3.11, Saving Firm B, Role: Physician .............................. group copies
Master 3.12, Report Form for Firm B .................................. student copies and transparency
Master 3.13, Some New Information about Firm B .................... group copies

Lesson 4, Are You Susceptible?
Master 4.1, Rolling the Dice ........................................ student copies
Master 4.2, Thinking about the Game ................................ student copies
Master 4.3, High Genetic Risk ........................................ class copy
Master 4.4, Moderate Genetic Risk .................................... class copy
Master 4.5, Low Genetic Risk ......................................... class copy
Master 4.6, Genetic Protection ........................................ class copy

Lesson 5, Making Decisions in the Face of Uncertainty
Master 5.1, Making Decisions in the Face of Uncertainty .......... student copies (print version only)
Master 5.2, Analyzing the Issues ..................................... student copies
Master 5.3, Reference Database ..................................... student copies (print version only)
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

Name(s) ______________________________________________________________ Date ______________

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 GAG GAG AAG TCT GCC GTT ACT GCC CTG TGG GCC AAG GTG
AAC GTC GAT GAA CTC CTG AAG GGC TCG ACG GGC ACG AAG GTC TAC TGC CTT GAC TCT
```

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 GTG GAG AAG TCT GCC GTT ACT GCC CTG TGG GCC AAG GTG
AATACCAATAGAAACTGGGCAATGGAGCCAGAAGGACTAGTTTGATCTATAGGCACACTGACTCTCTCTGCTTATT
GGTCTATGGGAC

The sequence is continued on the next page.
```
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 calculated applies across the entire genome. How many total base differences would you expect to find between person A and person B?
   \[
   3,000,000,000 \times _____ = ____________ \text{ total differences}
   \]
   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:

   \[
   \frac{\text{number of different students}}{\text{total number of students}} = \frac{30}{150} = 0.2
   \]

2. Convert this result to a percentage by multiplying by 100: 0.2 × 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?

   \(3,000 \times 20% = 600 \text{ different students}\)

Master 2.3

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 husband, 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. Depending on whether or not you have access to the Internet, use either the online documentary “What Is Sickle Cell Disease?” and Sickle Cell Database or Master 2.5, Reference Database: Sickle Cell Disease—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 Hb A?

   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 information provided on the handout your teacher will give you to determine the results of the test.

3. Write the dialogue for a brief scene (2–3 minutes) 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.
Sickle Cell Disease—Definition

Sickle cell disease is a genetic disorder that affects approximately 1 out of every 625 African Americans in the United States. It is caused by a single amino acid change in a protein called hemoglobin.

Hemoglobin is the major protein inside red blood cells. Its primary function is to transport oxygen. When the oxygen concentration in the blood decreases, the defective hemoglobin molecule forms long crystals inside the red blood cell. These crystals cause the red blood cells to elongate and assume a “sickle” shape. The crystallized hemoglobin also damages the cell membrane so that the cells become very fragile.

Sickle Cell Disease—Incidence (Africa)

In some parts of Africa, about 4 percent of black Africans have sickle cell disease.

Why does sickle cell disease occur more frequently among black Africans than among African Americans? Scientists believe that this difference is related to the threat of a fatal form of malaria that occurs in many parts of Africa. Studies reveal that people who are homozygous for the normal allele for hemoglobin (Hb A/Hb A) often die of malaria. However, people with sickle cell trait (people who are heterozygous, Hb A/Hb S) do not contract the fatal form of malaria. Thus, more heterozygotes live than do people who are homozygous for the normal allele, and these people often pass the sickle cell allele on to their children. This phenomenon keeps the incidence of the sickle cell allele in the population higher than it would be if there were no threat of malaria.

Sickle Cell Disease—Incidence (United States)

About one-quarter of 1 percent (0.25%) of African Americans are homozygous for the sickle cell hemoglobin allele and have sickle cell disease.

Why is the incidence of sickle cell disease in the United States so low? It is low because people with sickle cell disease often die in childhood or early adulthood, before they have had children. Thus, many people with sickle cell disease do not pass this allele on to children. Instead, most inheritance of the allele is from a parent who is heterozygous for the allele to one or more of his or her children.

Sickle Cell Disease—Inheritance

Sickle cell disease results when a person inherits an allele for sickle cell hemoglobin from each of his or her parents. This inheritance pattern means that the person is homozygous for sickle cell hemoglobin and that his or her body does not produce any normal hemoglobin, only sickle cell hemoglobin.

Geneticists show the inheritance pattern of sickle cell disease by using symbols to represent the allele for normal hemoglobin (Hb A) and the allele for sickle cell hemoglobin (Hb S). A person with normal hemoglobin has inherited one allele for normal hemoglobin from each parent and so has the genotype Hb A/Hb A. In contrast, a person who has sickle cell disease has inherited one sickle cell allele from each parent and has the genotype Hb S/Hb S.

But what about a person who inherits an allele for normal hemoglobin from one parent and an allele for sickle cell hemoglobin from the other parent? This person has the genotype Hb A/Hb S and is said to have sickle cell trait. Although some of the hemoglobin in this person’s body is sickle cell hemoglobin, the rest of the hemoglobin is normal, and the person usually exhibits no symptoms of the disease.
Sickle Cell Disease—Structure of Altered Hemoglobin

The hemoglobin that is made in the bodies of people with sickle cell disease (Hb S) differs from normal hemoglobin (Hb A) in just one amino acid. In normal hemoglobin, this amino acid is a glutamic acid. In sickle cell hemoglobin, it is a valine.

Sickle Cell Disease—Symptoms

People with sickle cell disease may experience symptoms such as severe pain, fever, and even death. These symptoms occur when the misshapen red blood cells that form under conditions of low oxygen concentration clog blood vessels and burst.

Such patients frequently experience a vicious cycle of events called a “sickle cell disease crisis” in which low oxygen concentration causes sickling, which causes ruptured red blood cells, which in turn, causes even lower oxygen concentrations in the body and still more sickling and red blood cell destruction. This process leads to a serious loss of red blood cells within a few hours and can cause death.

Sickle Cell Disease—Testing

Normal hemoglobin (Hb A) and sickle cell hemoglobin (Hb S) differ in just one amino acid. Hb S has valine in the position where Hb A has glutamic acid. This difference results from a difference between the DNA sequence of the allele that codes for normal hemoglobin and the sequence of the allele that codes for sickle cell hemoglobin.

The difference in one amino acid between Hb A and Hb S causes a difference in the electrical charge of the two forms of hemoglobin. Hb A has a greater negative charge than Hb S. This difference can be used to distinguish Hb A and Hb S in a process called electrophoresis. Hemoglobin from individuals suspected of having sickle cell disease or sickle cell trait is placed on a gelatinous slab (gel) beside standards of Hb A and Hb S. An electrical charge is applied across the gel, and the proteins move through the gel toward the positive end of the electrical field at a rate based on their size and charge. Because Hb A has a greater negative charge than Hb S, it will move further through the gel. After electrophoresis, the gel is removed and stained with a solution that adheres to proteins, revealing “bands” of stain at the positions to which the hemoglobin has migrated.

Doctors diagnose sickle cell disease by comparing the banding position of hemoglobin from an individual with the banding positions of Hb A and Hb S standards. An individual who is homozygous for Hb A will have only one protein band on the gel, at the same position as the Hb A standard, whereas an individual who is homozygous for Hb S (and has sickle cell disease) will also have one protein band on the gel, but at the same position as the Hb S standard. A heterozygous individual will have two protein bands, one at each position.
Results of the Lindsey Test

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

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 biostatisticians.* 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 symptoms associated with asthma. The results were inconclusive. 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.
You are an experienced physiologist* 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 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 typically are treated with drugs called bronchodilators. 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 muscle in the lungs. This causes the muscles to relax and the bronchioles to expand.

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* A physiologist studies the basic processes of life, such as respiration, digestion, circulation, and cellular metabolism.
** 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: 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 scientists 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 (pronounced 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 variants of the gene (non-E4 versions 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:

<table>
<thead>
<tr>
<th>Genotype, Based on ApoE Type</th>
<th>None</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2/E2&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>E3/E3&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>E4/E4&lt;sup&gt;1&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> These genotypes are uncommon.
<sup>2</sup> This genotype is common.

---

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

** 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.

Master 3.4

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 taking this problem so seriously. You decide you'd better learn something about the problem before the meeting. Using the company's database, you call up the test results on the drug and study them carefully.

Table 1. Effect of Drug X on Wheezing Associated with Asthma in 300 Children (Preliminary Results)

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of Children</th>
<th>Percentage of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>significant relief</td>
<td>102</td>
<td>_____%</td>
</tr>
<tr>
<td>some relief</td>
<td>128</td>
<td>_____%</td>
</tr>
<tr>
<td>no relief</td>
<td>70</td>
<td>_____%</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>100%</td>
</tr>
</tbody>
</table>

1. Calculate the percentages by dividing the number of children in each row by the total number of children (300). Record the percentages where indicated in the table.

2. Why do 70 children experience no relief of asthma symptoms after using Drug X?

3. Could it be related to the sex of the child? Could it be related to whether the child has a pet.

* 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.
We analyzed additional data from the study to answer these two questions. Can we answer the questions now?

Table 2. Effect of Sex on Response to Drug X among 300 Children

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of Girls</th>
<th>Percentage of Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>significant relief</td>
<td>51</td>
<td>______%</td>
</tr>
<tr>
<td>some relief</td>
<td>67</td>
<td>______%</td>
</tr>
<tr>
<td>no relief</td>
<td>36</td>
<td>______%</td>
</tr>
<tr>
<td>Total</td>
<td>154</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of Boys</th>
<th>Percentage of Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>significant relief</td>
<td>51</td>
<td>______%</td>
</tr>
<tr>
<td>some relief</td>
<td>61</td>
<td>______%</td>
</tr>
<tr>
<td>no relief</td>
<td>34</td>
<td>______%</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>100%</td>
</tr>
</tbody>
</table>

1. Calculate the percentages by dividing the number of children in each cell by the total number of children (154 for girls; 146 for boys).

2. Based on the data above, does sex explain why some children experience no relief from symptoms of asthma after using Drug X? Why or why not?

Table 3. Effect of Exposure to Pet Dander* on Response to Drug X among 300 Children

<table>
<thead>
<tr>
<th>Response</th>
<th>Number with Pets</th>
<th>Percentage with Pets</th>
</tr>
</thead>
<tbody>
<tr>
<td>significant relief</td>
<td>42</td>
<td>______%</td>
</tr>
<tr>
<td>some relief</td>
<td>51</td>
<td>______%</td>
</tr>
<tr>
<td>no relief</td>
<td>27</td>
<td>______%</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>Number without Pets</th>
<th>Percentage without Pets</th>
</tr>
</thead>
<tbody>
<tr>
<td>significant relief</td>
<td>60</td>
<td>______%</td>
</tr>
<tr>
<td>some relief</td>
<td>77</td>
<td>______%</td>
</tr>
<tr>
<td>no relief</td>
<td>43</td>
<td>______%</td>
</tr>
<tr>
<td>Total</td>
<td>180</td>
<td>100%</td>
</tr>
</tbody>
</table>

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

1. Calculate the percentages by dividing the number of children in each cell by the total number of children (120 for those with pets; 180 for those without pets).

2. Based on the data above, does exposure to pet dander explain why some children experience no relief from symptoms of asthma after using Drug X? Why or why not?
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 happening 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 about Firm A

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

Number (and percent) of Subjects and Extent of Relief by Genotype

<table>
<thead>
<tr>
<th>Genotype, as Indicated by Amino Acids*</th>
<th>Significant Relief</th>
<th>Some Relief</th>
<th>Little Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>arginine/arginine</td>
<td>80 (78%)</td>
<td>20 (16%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>arginine/glycine</td>
<td>20 (20%)</td>
<td>100 (82%)</td>
<td>24 (35%)</td>
</tr>
<tr>
<td>glycine/glycine</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>38 (54%)</td>
</tr>
<tr>
<td>Total</td>
<td>102</td>
<td>122</td>
<td>70</td>
</tr>
</tbody>
</table>

* Molecular biologists have determined that a particular protein acts as a receptor for Drug X. 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, arginine/arginine) because each person has inherited two genes that encode the receptor protein.
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 assignments 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 president 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.
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 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 don’t know much about cystic fibrosis, so you pull out a medical textbook 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 gastrointestinal tract, and the ducts of the pancreas. CF causes the body to produce abnormally thick, sticky mucus that clogs these passages. The most characteristic symptom of CF is the excessive production of mucus in the airways and lungs. This mucus provides an ideal breeding ground for many microorganisms, and CF patients have frequent airway infections that can require hospitalization 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, 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.

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 treatment of cystic fibrosis. You know that Drug Y, your company’s major product, is widely used as a treatment 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 transmembrane conductance regulator (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 and controls the movement of chloride ions out of the cells. Depending on the specific type of CF mutation a patient has, the CFTR 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 interested 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 (CF). 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 CF 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 companies’ products to treat CF. 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 Cystic Fibrosis

<table>
<thead>
<tr>
<th>Major Type</th>
<th>Description</th>
<th>Primary Benefit</th>
<th>Treatment Addresses Symptoms or Cause?</th>
</tr>
</thead>
<tbody>
<tr>
<td>chest physical therapy</td>
<td>vigorous tapping on the back and chest with cupped hands</td>
<td>dislodges mucus from lungs, allowing better breathing and reducing the risk of infection</td>
<td></td>
</tr>
<tr>
<td>antibiotics</td>
<td>antibiotics administered intravenously, through pills, or, in the case of Drug Y, as a medicated vapor that is inhaled</td>
<td>treats lung infections that can damage the lungs and even cause death</td>
<td></td>
</tr>
<tr>
<td>enzyme supplements</td>
<td>supplements of pancreatic enzymes</td>
<td>improves digestion</td>
<td></td>
</tr>
<tr>
<td>diet</td>
<td>enriched diet and supplements of vitamins and other nutrients</td>
<td>reduces malnutrition and improves growth and development</td>
<td></td>
</tr>
</tbody>
</table>
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, Master 3.8)?

2. Describe cystic fibrosis (CF) in your own words (refer to the Physiologist handout, Master 3.9).

3. What have we learned in the past few years about the cause of CF (refer to the Molecular Biologist handout, Master 3.10)?

4. What is Drug Y (and most other current treatments) designed to do for CF patients (refer to the Physician handout, Master 3.11, 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?
I just heard from a colleague that another research team (not associated with our company) 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-citizen 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

<table>
<thead>
<tr>
<th>Heart Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

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 years)
(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.

* Be sure to check your record on Master 4.1a.
Life Stage 3: Choices as a Senior Citizen (Over Age 50 years)
(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. 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 (subtract 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.

* Be sure to check your record on Masters 4.1a and 4.1b.
Thinking about the Game

Name(s) ______________________________________________________________ Date ______________

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.

Results of the Game with or without Genetic Factors

<table>
<thead>
<tr>
<th>Review—Risk from Behavioral Choices Only</th>
<th>Recalculate—Risk from Genes and Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Stage 1: Teen years</td>
<td>Relevant genes</td>
</tr>
<tr>
<td>Life Stage 2: Adult years</td>
<td>Life Stage 1: Teen years + _______</td>
</tr>
<tr>
<td>Subtotal</td>
<td>Subtotal</td>
</tr>
<tr>
<td>Life Stage 3: Senior-citizen years</td>
<td>Life Stage 3: Senior-citizen years + _______</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
</tr>
</tbody>
</table>

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

You have a parent or sibling who had a fatal heart attack.

ADD 40 HEART POINTS.
Moderate Genetic Risk

You have an aunt or uncle who had a fatal heart attack.
ADD 10 HEART POINTS.
Low Genetic Risk

There is no history of fatal heart attacks among your close relatives.
ADD NO HEART POINTS.
Genetic Protection

You have high HDL-cholesterol levels.

SUBTRACT 10 HEART POINTS.

BUT IF YOU SMOKE, SUBTRACT NO POINTS.
Making Decisions in the Face of Uncertainty

Characters
- Beth
- Charlie, Beth’s husband
- Genetic Counselor (GC)
- Mother, Beth’s mother
- Jennifer, Beth’s daughter

Segment 1: Considering the Test
Beth and Charlie at home

Charlie: Something is bothering you, Beth. What is it?

Beth: I just read a newspaper article about a test for a breast cancer gene. I guess with Mom’s diagnosis, I’m worrying about it.

Charlie: But she’s a lot older than you.

Beth: When mom was first diagnosed with cancer when she was my age. I remember it, I was 13 years old. It wasn’t easy. And I never told you my grandmother died from ovarian cancer.

Charlie: So what did the article say?

Beth: Apparently there is a special kind of cancer that runs in families. If you have a certain form of this gene, you’re at a high risk of getting breast cancer. Now they have a test for it.

Charlie: What do they mean . . . high risk?

Beth: I don’t know. At least you know that you’re more susceptible. Or you find out that you’re safe.

Charlie: (Kindly) So go get the test if it’ll put your mind at ease.

Beth: But that’s just it. I don’t know if it would make me feel safer. What if I find out that I do have it? I’ll feel doomed.

Charlie: I think we should find out. As soon as possible. You’ve got a cloud hanging over you as it is.

Beth: A cloud! Do you know how worried I’ve been all these years? That’s why I was so confused about taking birth control pills. At first, they thought it would increase the risk of getting breast cancer, so I didn’t take them. Now, I read that it can actually lower the risk of ovarian cancer.

Charlie: Wouldn’t you feel better if you knew for sure about that gene?

Beth: I just don’t know.
Segment 2: A Family Question

Beth's mother, Beth and a genetic counselor at the genetic counselor's office

GC: I'd like to make sure we all understand what we are here to discuss.

Mother: It's because of me, isn't it?

GC: Beth is interested in having the BRCA1 and 2 genetic tests. These tests help us identify women who have a genetic predisposition toward breast cancer and we find that we can get more information to help us understand Beth's situation if we first test family members who already have cancer.

Mother: I've already been through the ringer with this disease. What possible good is this test going to do for me?

Beth: This test is for me mother. I have a right to know . . . And for the sake of my family.

Mother: I'm already the family outcast, the one with this condition, who has passed it on to all of you.

Beth: No one is blaming you mother. This is just something our family has to deal with.

GC: Let's not get ahead of ourselves. The first step is to understand what such a test can tell you and then decide if this is information that you want to know.

Mother: What if the family doesn't want to deal with it. Your sisters, aunts and cousins might not want to know all this stuff. It'll be one more thing to have a big family ruckus over.

GC: You will decide who you want to tell. Now we will encourage you to tell your relatives because the information can be useful to them regardless of the result. I can help you think about how to tell them if you decide you want to.

Mother: And if I take the test and it turns out that my cancer was related to one of these mutations, what will you do?

Beth: Well, I'd continue to watch carefully for any signs of cancer, and I'd get Jennifer tested. She's my teenage daughter.

GC: I can understand your concern about your daughter. But there are several reasons why we do not offer testing to children under 18 years of age. The foremost being, that the test results won't change the care we give Jennifer.

Mother: The world has gotten so complicated. I don't know that more information is better. But you are right, I should get tested so that you can have a better idea of what to do. My sister has been wondering if she's at risk as well. After everything I've been through, I'll be able to handle this information.

Beth: I really appreciate this mom. I want to know. I'll either be relieved, or I'll have something real to worry about.
Segment 3: The Test Results

Beth and the genetic counselor in the genetic counselor’s office

GC: Beth, the tests show that you and your mother have the BRCA1 mutation.

Beth: Hmm. I had a feeling about this after my mother’s test was positive. So what does this mean for my family and me?

GC: Two things. For your family, it means that you could pass this mutation to your children. For your own health, it means you have an increased risk of developing breast and ovarian cancer and possibly at a younger age.

Beth: Is there anything I can do about it, to improve my odds?

GC: You can continue to watch yourself closely and get regular checkups. We might want you to start having mammograms earlier than you normally would. If you do develop cancer, early detection greatly improves your chances that the treatment will be effective. In addition, some people consider preventive surgery, but that is a tougher decision to make.

Beth: I see. I know my sister is going to want to get tested. If her results are negative does that mean she is safe?

GC: If she doesn’t have the mutation then she probably has about the same risk of developing breast cancer as other women without the mutation.

Beth: What about my children?

GC: Your son and daughter each have a 50 percent chance of having the mutation we see in your family. You probably will want to think about whether you want to share this information with them. Nothing at this time indicates that we would change their medical care in any way.

Beth: You’re right. I need to think about all of this for a while. Jennifer would probably want to know. But my son is only 12. It might cause him to worry rather than help him.

GC: Take your time adjusting to this news. We can meet again to discuss how you’re doing and what you want to tell your children. Do you have any concerns?

Beth: It’s just that now I feel so different from other people.

GC: Everyone is different. Just as people vary in their physical appearance, they also vary in their susceptibility to disease. What you are feeling is perfectly normal. It may take a while for you to accept it. Give yourself some time. Talking with some of your family members, even your mother, may help.

Beth: At least now I know some of the cards I’ve been dealt.
Segment 4: A Diagnosis of Breast Cancer

Beth and Charlie three years later, in the living room

Charlie: I felt the oncologist was encouraging. It’s really good that we caught it early.

Beth: Ever since Mom got her results, I knew I was going to have the mutation too. I knew this was going to happen.

Charlie: Well, it’s just the roll of the dice.

Beth: Yeah, just chance . . . It was a relief that Aunt Susan tested negative for both genes. At least my cousins don’t have to worry. And now that I know that I have cancer, I’m actually a little relieved.

Charlie: Relieved?

Beth: Now I can focus on something specific. You know, I’d been thinking about having both my breasts removed, even before the cancer. Now I have a real reason to do it.

Charlie: Beth, you’ve got to stay positive. Medicine is getting better. They have a whole treatment plan worked out for you. They said there wasn’t any trace of cancer in your other breast.

Beth: But the risk is high.

Charlie: Well, we have time to decide about that.

Beth: I know Jennifer is going to take this hard.

Charlie: She’s a strong girl.

Beth: You know, we probably should tell her about my positive gene test too. I know we felt that she was too young when I got tested, but maybe now maybe she really should get the test.

Charlie: She’s barely 19, she’s doing so well in college. This is going to be a lot for her to handle all at once.

Beth: But I wanted to know everything I could.

Charlie: She’s still young. We’ve got some breathing room. Let’s just take things one step at a time.
Segment 5: Five Years Later

Beth and Jennifer in the kitchen

Jennifer: You seem to be back to your old self.

Beth: Yeah, I feel good. I didn't know it would take so long for my energy to come back.

Jennifer: You look great too.

Beth: Thanks. It's been a year since the lumpectomy and so far it looks like I've been cured. How about you? Have you given any more thought to the test?

Jennifer: Sure, I think about it. I'm young and I live my life like I'm at a high risk anyway.

Beth: You've been doing the self-checks?

Jennifer: Of course, once a month. And I go to the doctor twice a year. The nurses even know the name of my cat.

Beth: We were so worried about how you'd handle all this information.

Jennifer: Well, now I'm more worried about what other people know about me.

Beth: Other people like whom?

Jennifer: You know I've started interviewing for jobs.

Beth: They can't ask you about personal stuff, can they?

Jennifer: Maybe not, but after I'm hired I want to make sure that I get my health insurance. I don't want to go in with this test on my record.

Beth: That sounds like discrimination.

Jennifer: For the insurance companies, it's just business. Anyway, I just don't need to know about this gene, at least not now.

Beth: It's up to you, but I can't help still being your mother.
Analyzing the Issues

Use this worksheet to take notes while you either watch the video Making Decisions in the Face of Uncertainty a second time or reread the dialogue on Master 5.1, segment by segment. 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.
Breast Cancer—Causes
A person's cells contain a variety of genes that normally work together to control cell division so that more cells are produced only when the body needs them. The transformation of a cell from normal to cancerous requires that the cell experience several separate changes (mutations) in the genes that control division. When such changes occur in breast or other tissue, cells keep dividing even when new cells are not needed, and a tumor may form.

Breast Cancer—Definition
Cancer is a group of more than 100 diseases that occur when cells become abnormal and divide without control or order. This abnormal division may produce a tumor that can be benign (not cancerous) or malignant (cancerous). Malignant tumors can invade, damage, and destroy nearby tissues and spread to other parts of the body.

There are several types of breast cancer. The most common begins in the lining of the milk ducts of the breast. Another type begins in the lobules where milk is produced. If a malignant tumor invades nearby tissues (for example, lymph nodes in the area), it is known as invasive cancer.

Breast Cancer—Detection
The earliest sign of breast cancer is usually an abnormality that shows up on a mammogram (a special X-ray of the breast) before it can be felt by the woman or a healthcare provider. When breast cancer has developed to the point where physical signs and symptoms exist, these symptoms may include a lump, thickening, swelling, distortion, or tenderness in the breast, or skin irritation or dimpling.

The value of mammography is that it can help healthcare workers identify breast abnormalities that may be cancer at an early stage before physical symptoms develop. Many studies have shown that early detection increases survival and expands treatment options.

Most breast lumps are not cancerous, but only a physician can determine this. When a woman has a suspicious lump, or when a suspicious area is detected on a mammogram, further tests are typically done to make a definite diagnosis.

Breast Cancer—Incidence
Breast cancer is the most frequently diagnosed nonskin cancer and the second most common cause of death for American women. Approximately 178,000 new cases of invasive breast cancer were expected to be diagnosed in the United States in 1998. This number translates to an incidence rate of about 110 cases per 100,000 women. About 1,600 new cases of invasive breast cancer were expected to be diagnosed in men.

Breast Cancer—Managing Risk
What are the options available to a person who is found to have a mutation in a BRCA1 or BRCA2 gene? The National Cancer Institute (NCI) lists the following options:
**Surveillance.** If cancer develops, it is important to detect it as soon as possible. Surveillance methods for breast cancer may include mammography and a clinical breast examination. Some health professionals recommend self-examination, but this should not be used to replace clinical exams. Surveillance for ovarian cancer includes pelvic ultrasound, certain blood tests, and clinical examination. Surveillance can sometimes help detect cancer at an early stage, but it does not guarantee a cure if cancer is found.

**Prophylactic surgery.** This type of surgery involves the removal of as much of the at-risk tissue as possible in order to reduce the chances of developing cancer. Preventive mastectomy (removal of healthy breasts) and oophorectomy (removal of healthy ovaries) are not, however, a guarantee against developing cancer.

**Risk avoidance.** Particular behaviors that are believed to decrease cancer risk include limiting alcohol consumption and increasing regular exercise. Research results on the benefits of these behaviors are based on studies in the general population; the effects of these actions on people with BRCA1 or BRCA2 mutations are unknown.

**Chemoprevention.** This approach uses medication (such as tamoxifen) and micronutrients (such as dietary retinoids, vitamin E, and selenium) to reduce the risk of developing cancer. Tamoxifen is a drug used to prevent a recurrence of cancer in women who already have been diagnosed with cancer. In these women, tamoxifen has also been shown to reduce the risk of new cancers from developing in the other breast. Studies are currently underway to determine whether high-risk women in the general population can benefit from taking tamoxifen as a prevention for breast cancer.

**Gene therapy.** At present, mutated genes cannot be repaired. Some day, however, it may be possible to fix or manipulate the genes or sets of genes that cause or increase one’s risk of cancer and other diseases.

**Breast Cancer—Related Genes**

Approximately 5 to 10 percent of women with breast cancer have a hereditary form of the disease. These women have inherited an altered form of one of the several genes involved in the control of cell division. For example, scientists believe that inherited mutations in the BRCA1 and BRCA2 genes are involved in 30 to 70 percent of all inherited cases of breast cancer. Although inheriting one of these mutated genes does not guarantee that a woman will develop breast cancer, it does increase her risk.

Scientists now have tests that can detect mutated BRCA1 and BRCA2 genes with 90 to 95 percent accuracy. Current technology has limited sensitivity and will miss some mutations. However, when someone with a cancer diagnosis and a family history of the disease has been tested and found to have a mutated BRCA1 or BRCA2 gene, the family is said to have a “known mutation.” Others in the family can now be tested to see if they have that mutation. Once a mutation is identified within a family, the testing of relatives at risk is close to 100 percent accurate.

A positive test indicates that a person has inherited a known BRCA1 or BRCA2 mutation and has an increased risk of developing breast and ovarian cancer. In addition, evidence from several studies has shown that a man with a mutated BRCA1 or BRCA2 has a small increased risk of developing prostate cancer. However, a positive result only provides risk information and does not indicate whether or when cancer might develop. A positive result also does not provide any information about how a woman will respond to medical treatment should cancer be diagnosed. **It is important to note that many, but not all, women who inherit a mutated BRCA1 or BRCA2 gene will develop breast or ovarian cancer.**
Both men and women who inherit a mutated gene, whether or not they develop cancer themselves, can pass the mutation on to their sons and daughters.

A negative BRCA1 or BRCA2 test will be interpreted differently, depending on whether a family mutation is known. If a known mutation is not found in certain family members, those individuals do not have an increased risk for breast cancer based on family history and cannot pass the family risk on to their children.

However, in cases where no BRCA1 or BRCA2 mutation has previously been identified in a family, a negative test is not very informative. It is not possible to tell whether the person actually has a mutation but the test missed it (false negative) or whether the result is a true negative. Furthermore, a woman may have a mutation in a gene other than BRCA1 or BRCA2 that increases her cancer risk, but is not detectable by this test.

Breast Cancer—Risk Factors
Overall, American women have a 1 in 8 chance of developing breast cancer sometime in their lifetimes.

No one knows why some women develop breast cancer and others do not. Over the years, however, researchers have identified certain characteristics, called risk factors, that influence a woman’s chance of developing the disease. For example, the risk of developing breast cancer increases with age. The risk also is higher in women who have a personal history of breast cancer or a family history of breast cancer. Other factors that can increase a woman’s risk of developing breast cancer include early onset of menstruation, late menopause, recent use of oral contraceptives, and never having children or having the first live birth at a late age.

Most women will have one or more risk factors for breast cancer. However, many women who develop breast cancer have no known risk factors other than growing older, and many women with known risk factors do not get breast cancer.

Breast Cancer—Survival
The five-year survival rate for localized breast cancer (cancer that has not spread) has increased from 72 percent in the late 1940s to more than 95 percent today.

If the cancer has spread regionally, however, the five-year survival rate is 76 percent. If it has spread to distant sites, the rate is 21 percent.

Breast Cancer—Treatment
Depending on the medical situation and the patient’s preference, treatment may involve lumpectomy (removal of the tumor) and removal of the lymph nodes under the arm; mastectomy (removal of the breast) and removal of the lymph nodes under the arm; radiation therapy; chemotherapy; or hormone therapy. Sometimes two or more treatment approaches are used in combination.