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GENETIC RESEARCH: MINING FOR MEDICAL TREASURES

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COVER IMAGE: The cover image is a spectral karyotype, or SKY, of human chromosomes. Spectral karyotyping is a new technique that allows the simultaneous discernment of all 23 pairs of chromosomes. SKY uses a series of specific probes, each with varying amounts of fluorescent dyes. A computer program detects slight variations in color that are undetectable by the human eye. The computer then reassigns an easy-to-distinguish color to each pair of chromosomes, resulting in a full-color digital image like the one seen here. SKY makes it easier to sort chromosomes because homologous pairs are the same color. In addition, disease-related aberrations in chromosomes are more easily recognizable. (This image provided courtesy of Dr. Thomas Ried, National Cancer Institute, MD.)
Genetic Research: Mining for Medical Treasures
By Cathryn Delude

Genes Make the Headline News

"News Flash! Obesity Gene Identified!"
Increasingly, headlines announce newly discovered links between genes and their functions in the body. Ironically, in 1953 the papers barely carried the news that James Watson and Francis Crick had elucidated the structure of DNA, the bearer of all genetic information. At that time, no one knew how to mine the genes buried in our DNA. Since then, scientists have pinpointed thousands of genes, including defective genes responsible for rare inherited diseases like Huntington disease. Researchers have established links between genes and common diseases not previously considered genetic conditions, such as cancer. They have associated genes with psychological and personality traits, including schizophrenia and impulsivity, as well as human capabilities, such as language. This genetic research promises to improve our ability to diagnose, prevent and treat diseases and disorders. Fifty years after Watson and Crick’s breakthrough, scientists are publishing the “final draft” of the human genome, which is the entirety of DNA in our 23 pairs of chromosomes. The complete blueprint of our genome will reveal more unknown genes and undoubtedly lead to more breaking news.

What do these discoveries mean? Usually, they mean that a genetic mutation or variation is correlated with a defect or disorder. The normal function of many genes remains unknown, but certain genetic variations occur more frequently among people with a family history of a disorder. Such genes fall into the category of risk factors rather than direct causes. Most conditions are multigenic (influenced by many genes) rather than monogenic (caused by a single
gene like Huntington and cystic fibrosis). Furthermore environmental or lifestyle influences (diet, exercise, toxins, infections, smoking, and prenatal nutrition) orchestrate how a genetic score is played out in an individual’s life.

Each genetic discovery is a piece of the complex biological puzzle that researchers are seeking to solve. It is not an end unto itself, but the beginning of an effort to learn how and why specific genetic variations affect the health and/or development of an individual. This basic research lays the foundation for practical applications that will increasingly affect our lives and health care.

**Basic Genetic Research**

The notion that traits are inherited was not new when the Austrian monk Gregor Mendel began his experiments with peas in the 1860s. Folklore abounds with references to inheritability: “Like father, like son.” However, Mendel was the first to conduct controlled experiments on the inheritance of specific traits: white or red flowers, tall or short stalks, etc. He defined two main inheritance patterns: dominant and recessive. Mendel discerned that the hereditary traits do not mix or blend; they are inherited in discrete units that he called “factors” and we now call genes.

His work was ignored until 1900, when several scientists rediscovered his research. They realized that the dominant and recessive inheritance patterns

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**Figure 1:** ILLUSTRATION OF DOMINANT AND RECESSIVE INHERITANCE PATTERNS. Each gene comes in a pair, and offspring inherit one copy from each parent. Different versions (alleles) of a gene produce variations in a trait, and sometimes disease. For a dominant monogenic disease, only one copy is needed to cause disease. If one parent has the disease, approximately 50 percent of the offspring will have it. For recessive traits, two copies are needed. If both parents carry one copy, they are unaffected carriers and they won’t exhibit the disease. However, approximately 25 percent of their offspring will receive two copies and will have the disease, while 50 percent on average will be unaffected carriers. *Designed by Corporate Press.*
defined by Mendel applied to some genetic diseases. For example, Huntington disease follows the dominant pattern; cystic fibrosis and sickle cell anemia follow the recessive pattern. (See Figure 1.)

Mendel’s work explained how some diseases are inherited, but not how a disease gene—or any genetic variation—came to be in the first place. Hermann Joseph Muller provided the answer in 1926. He exposed fruit flies to X-rays and observed how their offspring developed deformities. From that he deduced that genes can be chemically changed or mutated, and those genetic mutations can cause physical changes.

But how do mutations cause physical changes? Linus Pauling realized that genes are recipes for proteins, the assemblers and building blocks of cells. He knew that sickle cell anemia was a genetic disease. He discovered that it results from a defective hemoglobin protein in red blood cells and concluded that a defect in one gene produces the defective protein. Thus, mutations alter genetic recipes in DNA, which can result in altered and sometimes malfunctioning proteins.

Now the question was: What is a gene made of and how can it be altered? Scientists knew that chromosomes are the hereditary package, and that they are composed of both proteins and a long, monotonously repetitive

**Figure 2:** (A) DNA Illustration: A chromosome’s DNA is structured as a double helix and consists of four bases: A, T, C, and G (adenine, thymine, cytosine, and guanine). These DNA bases bind chemically to each other in complementary base pairs. A on one strand binds to T on the other, and C to G, to produce complementary strands. When cells divide, the strands separate and each strand attracts complementary bases to assemble a new complementary strand, so that each cell in the body receives a complete set of chromosomes. Designed by Corporate Press. (B) Photo of Watson and Crick: “We have discovered the secret of life.” – Francis Crick. James Watson and Francis Crick used this model of DNA to demonstrate its structure as a double helix composed of complementary base pairs. They shared the 1962 Nobel Prize with Maurice Wilkins for this discovery. Photo by A. Barrington Brown / Science Photo Library.
molecule called DNA (deoxyribonucleic acid). DNA is composed of just four chemical building blocks, called bases: A, T, C, and G for adenine, thymine, cytosine, and guanine. DNA seemed too simple to account for the complexity of heredity, so most scientists assumed that chromosomal proteins carry genetic information. However, by 1944 Oswald Avery, Maclyn McCarty, and Colin MacLeod proved in fundamental experiments using bacteria that it is DNA, not proteins, that stores an organism’s genetic material.

In the early 1950s, James Watson and Francis Crick were shown Rosalind Franklin’s X-ray crystallography photographs of DNA, and they deduced that DNA is composed of two chains or strands, running in opposite directions, that twist into a double spiral or helix. By April 1953, they had constructed a model of the molecular structure of DNA. Their model demonstrated how the four bases bind as complementary pairs. (See Figure 2.) From this structure, Watson and Crick proposed a mechanism for how DNA replicates itself. We now know that each human cell contains 3.2 billion base pairs packaged tightly as chromosomes inside a cell’s nucleus.

Crick realized that DNA comprised a coded language for genetic information. Marshall Nirenberg, Har Gobind Khorana and others deciphered that code, showing how the sequence of the bases in a gene translates into a specific protein. (See Figure 3.) Once this code was understood, it became clear that genetic mutations involved changes in the DNA sequence which can change the protein product. In sickle cell anemia, for example, just one base change (from A to T) results in defective hemoglobin.

Scientists knew that sequencing our DNA would lead them to the genes, but tackling the lengthy, repetitive strands of DNA was unimaginably cumbersome. Early on, researchers probed short sections of DNA base by base, keeping tabs on blackboards, and later used computers to store and ana-

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Figure 3: From Gene to Protein
A gene is a portion of a chromosome (A), made of DNA, that is translated into a functional product, usually a protein. A gene has coding regions called exons and non-coding regions called introns. When a gene is activated or expressed, the introns are cut out of the gene and the exons are transcribed into a related genetic language called messenger RNA (mRNA), which is the single-stranded complement of the original DNA sequence (B). The mRNA is shuttled to a protein-making factory called the ribosome, where it is read three letters at a time. These three letters are called codons, and each codon corresponds to one of twenty amino acids. The amino acids are linked into a chain, which then folds into a protein. The shape and chemical composition of the protein determines its function and how it interacts with other proteins and molecules. Ultimately, that form and function was determined by the order of the amino acids, which was determined by the mRNA sequence, which in turn was determined by the gene’s DNA sequence. Designed by Corporate Press.
In 1985, a collaboration of international researchers resolved to sequence the entire human genome using public funding from the National Institutes of Health and the Department of Energy, as well as private funding. The program known as the Human Genome Project (HGP) officially began in 1990.

The genome project is based on many years of basic research, much of it publicly funded, on DNA biochemistry, enzymes, information transfer within cells and on the development of precision tools. Completing this project became feasible only with giant progress in information technology and data management, known as bioinformatics, as well as improved technologies for accurately, rapidly and cost-effectively sequencing large sections of DNA. Sophisticated computer programs were developed to handle the massive data generated by the ever-more automated sequencing machines.

In the early 1990s, the HGP developed rough maps of human chromosomes with signposts or markers for the physical location of many known genes. In an action unprecedented in the scientific community, the HGP deposited sequence data every 24 hours in public databases, freely available to scientists around the world. The “first draft” of the human genome was published in February 2001, and a final draft is being prepared for publication in April 2003. Having the entire sequence of our DNA provides a “reference book” for how biology works at the molecular level.

In addition to the human genome, researchers are sequencing the genomes of model organisms used to study diseases and basic biological processes. This research is valuable, because the genetic language is universal: every organism uses the same DNA code. Furthermore, many genes involved in essential, common functions like metabolism and cellular division have been conserved over the evolutionary time scale: the DNA sequence of such genes has changed little as organisms evolved from common ancestors, so that even distantly-related species have similar versions. As a result, it is possible to study these genes in mice, worms, and bacteria and apply that knowledge to human biology. Scientists also “knock out” (inactivate) specific genes, or mutate them, to determine their role in an organism. Using such techniques, model organisms provide a valuable shortcut to understanding and possibly treating human diseases.

Recently, using gene “knock-out” and similar techniques, researchers have developed unique strains of mice that model specific human diseases, from arthritis to Alzheimer’s disease. Completion of the mouse genome in December of 2002 marked the first opportunity to compare the human genome with another mammal and afforded scientists some exciting insights. The mouse shares not only an extraordinary number of genes with us, but also large expanses of non-coding DNA. Scientists speculate that this non-coding DNA, which was once considered “junk,” may play a critical biological role after all. More recently, scientists discovered that some of these sections encode for snippets of RNA that regulate gene activity.

### What is a Genome?

The genome refers to the entirety of DNA in an organism. Humans have 46 chromosomes, organized in 23 pairs, with one chromosome in a pair coming from the mother and the other from the father. This DNA includes genes, which are sections that encode proteins. However, about 95–98% of the DNA in the human genome does not encode proteins. Some of this non-coding DNA helps regulate the activity of genes, but much of it has unknown functions. Each cell in the body includes a complete copy of the genome, although cells in a specific tissue activate only a subset of genes—those needed for that particular tissue. Scientists estimate that the human genome includes 30,000 to 40,000 genes. Many human genes are quite similar to genes in other species, and these similarities have accelerated the study of genomics. Scientists can identify the basic function of a gene in a worm, fruit fly or mouse, and thereby often understand its role in humans.
Manipulating this RNA in model organisms may accelerate our understanding of its genetic functions and provide new strategies for clinical intervention.

Simultaneously, researchers are mapping sites in the genome where the sequence varies from one individual to the next. The most common type of variation involves just a single DNA base (A, T, C, or G) and is known as SNP (single nucleotide polymorphism), pronounced “snip.” Of the estimated 6 million SNPs in the human genome, about 200,000 may occur in genes. Many of these are associated with disease processes or drug metabolism, which affects how well individuals respond to a drug or whether they experience negative side effects. Scientists are attempting to associate SNPs with a specific disease risk or drug response. They have discovered that SNPs usually belong to a “neighborhood” and are inherited along with a collection of SNPs. These collections form a limited number of common patterns known as haplotypes. Haplotype patterns are more easily identified than individual SNPs. Among other things, a map of haplotypes will assist the search for medically significant variations within human populations. Scientists anticipate that this research will usher in a new era of personalized medicine. (See later section.)

Furthermore, genomics is progressing in tandem with other new fields, including proteomics, which is a parallel effort to identify and analyze all the proteins encoded by the genome. Since proteins are the functional elements of the genome, proteomics will enhance our understanding of general biological processes and also highlight new targets for drug development and genetic engineering.

Basic research is enabling us to understand the underlying

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type of Test</th>
<th>Age Performed or Indication</th>
<th>Approximate # Tests Performed / Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU (Phenylketonuria)</td>
<td>Newborn Screening</td>
<td>Mandated by law in 50 U.S. states</td>
<td>~4 million/year (birthrate in U.S.) / 1:16,250</td>
</tr>
<tr>
<td>Biotinidase</td>
<td>Newborn Screening</td>
<td>Mandated in 1/3 of U. S. states</td>
<td>~1–1.5 million/year / 1:105,000</td>
</tr>
<tr>
<td>CF (Cystic Fibrosis)</td>
<td>Carrier Screening</td>
<td>Professional guidelines suggest testing for pregnant women (and then partners)</td>
<td>Increasing to million(s)/year / 1:3,300</td>
</tr>
<tr>
<td></td>
<td>Diagnostic Testing</td>
<td>Infancy to childhood after symptoms and routine testing</td>
<td>~ 100–200 new cases per year</td>
</tr>
<tr>
<td>Aneuploidy (Down Syndrome)</td>
<td>Prenatal Testing</td>
<td>High risk pregnancies, including maternal age of 35 plus years. Amniocentesis at 15–18 weeks. CVS at 10–12 weeks</td>
<td>~ 0.5 million / 1:1504</td>
</tr>
<tr>
<td>Fragile X Syndrome</td>
<td>Diagnostic Test</td>
<td>Childhood to adulthood to confirm cause of mental retardation</td>
<td>Proportion tested unknown / ~20,000 – 30,000 affected individuals</td>
</tr>
<tr>
<td>BRCA1 and BRCA2 (Breast Cancer Genes) Testing</td>
<td>Predispositional</td>
<td>Adolescence through adulthood to determine if genetic predisposition is high in women with positive family history</td>
<td>20–30 labs perform testing / ~50,000 carry BRCA1 or 2</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Diagnostic Test or Newborn Testing</td>
<td>Adolescence or adulthood to confirm symptoms of iron overloading; newborns / children tested if a family member is diagnosed</td>
<td>~12 labs perform testing /1:400</td>
</tr>
</tbody>
</table>
principles and mechanisms of life. Already, such research has improved the ability to test for aberrant genes in an individual and has initiated promising new directions in drug development and medical intervention. As is often the case, solid research leads to knowledge that can directly affect our health care system and ultimately our lives.

**Genetic Testing and Screening**

One application of genetic research is testing for genes associated with a disease or a risk of a disease. When testing does identify a risk, that knowledge may be used to improve a person’s medical outcome through early intervention and prevention. In some cases, it can alert us to personal risks or risks to an offspring, but not provide clear guidance about what to do or expect, because the ability to test for a disease gene often precedes the ability to treat that disease. In those cases, health care professionals must help patients understand the uncertainties and choices.

**PKU and Newborn Screening: Improving Health**

The first people to undergo routine genetic testing in our society are our youngest members. Across the nation, state public health departments screen 4 million newborns yearly for 4 to 40 genetic and congenital disorders. For several of these, prompt medical intervention can prevent disease or reduce the disabling effects.1

Newborn genetic testing began with phenylketonuria, or PKU, a rare but debilitating metabolic disorder caused by a recessive gene. That gene was not discovered until the 1980s, but the disease’s biochemical signature was recognized in the 1950s. Affecting infants lack a critical enzyme (phenylalanine hydroxylase) that aids in the metabolism of phenylalanine, an amino acid contained in food. Without the enzyme, phenylalanine builds

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1 For a complete list of these tests, see the National Newborn Screening Status Report at http://genes-r-us.uthscsa.edu/resources/newborn/screenstatus.htm.
up, causing severe mental retardation. PKU strikes about 1 in 20,000 infants born to parents who usually have no family history of the disease. In the early 1960s, Dr. Robert Guthrie developed a dietary formula to treat the disease and a diagnostic laboratory test that measures phenylalanine levels in an infant’s blood. In 1963, Massachusetts mandated PKU tests for all infants and the other 49 states eventually followed. Today, PKU testing is considered a model procedure for preventive health care because the test is accurate and the treatment is highly effective.

Cystic Fibrosis and Genetic Testing

According to folk wisdom, a midwife would lick a newborn’s forehead, and if it was salty, she warned the parents that the baby would not survive childhood. She was probably detecting cystic fibrosis (CF), the most common recessive genetic disease among Caucasians, striking about 1 in 3,300 children in the U.S. each year. Until the gene responsible for CF was discovered in 1989, no one could accurately determine who carried the gene or if a newborn baby was affected. Cystic fibrosis is caused by any of 1,000 known mutations in a gene called CFTR. Some mutations are more common than others, and the common mutations vary among ethnic groups.

Analysis of the CFTR gene product explained why CF causes salty sweat. Normally, it encodes a protein (called a chloride channel) that transports fluids and salts across the cell membrane. Mutations cause this protein to malfunction, so that cellular secretions are viscous and salty. In the lungs, thick mucous harbors life-threatening infections. Damage to the pancreas reduces digestive enzymes, leading to poor absorption of dietary nutrients and delayed growth.

If a child develops symptoms of cystic fibrosis, dietary and enzyme supplements can improve nutritional development and growth. Recent advances in the use of preventive antibiotics, anti-inflammatories and physical chest therapy have reduced damaging pulmonary problems, improved quality of life and extended average life expectancy of most patients.

Genetic tests can confirm the diagnosis of CF in a child and determine which mutation the child carries. However, the results cannot provide a definitive prognosis for an individual child. Some people have mild symptoms with quite a long life span; while others with the same mutation in CFTR have severe symptoms and early death.

Currently, there is no national policy on newborn screening for cystic fibrosis. Pilot studies in Colorado and Wisconsin show that medical intervention before the onset of clinical symptoms improves the child’s nutritional development in early childhood, but does not necessarily reduce lung injury. When future treatments arrive that definitively improve the disease outcome, testing of newborns for CF may become the norm.

The American College of Obstetrics and Gynecology recommends that women who are or hope to become pregnant be offered carrier testing for CF, so that couples may make informed reproductive choices. If the woman tests positive, meaning she is a carrier, her mate would also have to be a carrier in order to have a child affected with CF. Each of their children would have a 25% chance of having CF.

Carrier and prenatal testing can aid in family planning and thus can improve the quality of life and general welfare of the individuals involved. For untreatable recessive diseases that kill infants or children, genetic testing can eliminate the heartbreak of bringing a child into the world for a short life of unimaginable suffering. For example, testing for Tay Sachs among the Ashkenazi Jews has reduced the incidence of the disease, which was fairly com-

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2 Earlier estimates of 1 in 12,000 infants affected by PKU were based on Boston area statistics where the Irish population has a higher incidence.
mon within that population just 30 years ago, by 95%. Some individuals use carrier testing when deciding whom to marry or whether to adopt, while prospective parents may use prenatal testing to provide an informed basis for pre- and post-natal decisions. For diseases like cystic fibrosis that have a more variable and less tragic prognosis, genetic testing can present difficult decisions, since no one can yet predict how severely or mildly a child would be affected. The physician must be able to discuss these uncertainties and probabilities with patients, and families can benefit from options that are carefully presented.

Unlike traditional medical diagnostics, genetic testing reveals information not just about the individual, but possibly about relatives, as well. In the case of recessive diseases, a positive diagnosis in a child reveals that both parents are carriers of the disease and so may want prenatal tests during future pregnancies. In addition, the parents’ other children, as well as their siblings and other relatives, may also be carriers and may want that information when they make reproductive choices.

Genetic testing for disease exemplifies how genetic information changes what we know about ourselves and how we might modify our behavior in light of what we learn. It requires a new dynamic between doctor and patient in the area of informed consent, explaining both the risks and benefits prior to testing, and in the interpretation of the test results.

**Colon Cancer: Assessing Risk Factors for Late Onset Conditions**

Over 4,000 years ago an Egyptian doctor wrote: “If [feces] has gone down like black lumps you shall say…his belly is in a bad state, blistered.”

Black stools, stained by blood, may still be the first sign of colon cancer, in which the large intestine has malignant tumors. With 130,000 new cases of colon cancer in the United States yearly, early detection could prevent two thirds of colon cancer deaths, saving over 30,000 lives. Testing for fecal blood can catch some early cases, but not all. Colonoscopies are more accurate, but because they are invasive and may be uncomfortable or embarrassing, many people avoid them.

Colon cancer was the first cancer for which scientists identified the genetic mutations for both sporadic and hereditary forms. A mutation in a tumor suppressor gene called APC (adenomatous polyposis coli) initiates all colon cancer. Normally, APC functions as a tumor suppressor gene or cellular “brake,” inhibiting other genes that issue growth signals. When mutated, APC cannot control cell division. A second random mutation in a gene called ras makes the protein it codes for stick in the “on” position. Ras is an oncogene or “accelerator” that produces growth signals, so this mutation speeds up cell division and creates a polyp. A third and forth mutation allow that polyp to become a malignant tumor over the course of 20 to 30 years. (See Figure 5.)

However, researchers discovered that some cancers arise when cells accumulate mutations in a series of genes that normally coordinate orderly cell division. Most such mutations happen randomly during a lifetime, perhaps because of toxins, radiation or other environmental triggers, but some can be inherited. People who inherit a mutation in one of these genes are not fated to get cancer, because they must still acquire other mutations. But they have a higher risk and are more likely to develop cancer at an earlier age. They are genetically predisposed to cancer.

In sporadic colon cancer, a cell in the lining of the colon acquires a random mutation in the APC gene. The remaining 20% of colon cases are caused by three types of inherited mutations affecting the APC gene that can lead to cancer much earlier in life. (See table)

Hereditary nonpolyposis colon cancer (HNPCC) and familial colon cancer (FCC) increase the risk of polyps that progress to cancer in middle age. Early and frequent colonoscopies can detect the polyps, which can be removed before they become cancerous. In familial adenomatous polyposis (FAP), polyps carpet the colon and many become malignant. The polyps are too numerous to remove, so preventive therapy involves removal and reconstruction of the colon and rectum.

Because early detection can save lives, experts encourage physicians to inquire about a patient’s extended family history and, if indicated by that history, to offer genetic tests. Such tests can focus screening efforts on those at high risk, while family members without the genetic risk can be spared frequent colonoscopies and increased anxiety. In the future, doctors may be able to offer preventive therapies before polyps form.

Research characterizing the APC mutation has led to new techniques that can detect protein markers for a mutated APC gene without actually testing for genetic mutations. Normally, the APC gene produces a long protein, but the mutated gene results in a shorter, truncated protein. The presence of that truncated protein is evidence of the first stage of all colon cancers. Dr. Bert Vogelstein and colleagues are currently developing a procedure using that truncated protein as a marker for an early and non-invasive diagnosis of both hereditary and sporadic colon cancer. When clinically available, such tools will save lives by more effectively detecting early and still treatable colon cancers.

<table>
<thead>
<tr>
<th>Colon Cancer Risks and Age of Onset</th>
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<tbody>
<tr>
<td><strong>Type of Cancer</strong></td>
</tr>
<tr>
<td>Sporadic (not inherited)</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (HNPCC)</td>
</tr>
<tr>
<td>Familial colon cancer (FCC)</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (FAP)</td>
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</tbody>
</table>
Genetic tests for cancer and other late onset conditions pose ethical dilemmas. Without appropriate legislation a positive result might jeopardize health or life insurance and job security, and it may cause psychological stress. Furthermore, a positive result may mean that relatives are also at risk. Should they be offered the test? When? Should children be tested? It’s a difficult question. In FAP, polyps can occur in children as young as 10, progressing to cancer by the 20s. Health professionals must carefully explain these probabilities, focusing on the importance of prevention and early intervention.

Genetic testing for a predisposition to a late onset condition challenges society to develop fair and equitable practices. Meanwhile, the growing understanding of the genetic progression of diseases and their markers will inform new clinical diagnoses and better prognosis. Genetic testing may be expensive, but preventive measures to reduce long-term disease are an efficient use of resources.

What’s Ahead?

Genetic discoveries are rapidly increasing our understanding of how biological processes work at the molecular level, elucidating the causes of disease, not just the symptoms. This understanding could lead to more targeted, effective and individualized medical treatments.

Targeted Drug Therapy and Rationally Designed Drugs

Currently, most drugs interact with molecular or cellular targets that are involved in numerous biological processes. Because of these complex interactions, the drugs may produce unwanted and sometimes dangerous side-effects. Research in the areas of genomics and proteomics will lead to a greater understanding of disease, which in turn produces safer, more effective medicines. An early example is Gleevec, a drug introduced in 2001 to treat chronic myelogenous leukemia (CML). Scientists pinpointed a key protein made by a mutated gene. This protein signals an oncogene (tumor promoting gene) to trigger the runaway division of malignant white blood cells. Researchers designed a molecule that targets a notch that only appears in the mutated version of the protein. The molecule slips into the notch and jams the protein’s signal, but it does not interfere with the normal version of the protein in healthy cells. This rationally designed drug successfully reduces the cancer with fewer side effects than most chemotherapy, which attacks both malignant and healthy cells. Scientists are using this strategy for many other drug development efforts.

Another strategy is to repair or replace a defective gene, a process known as gene therapy.

Gene therapy is still in the early stages of clinical investigation and has had some adverse results. However, this approach holds great promise and may one day correct gene defects and in some instances actually provide cures.

Personalized Medicine for an Individual’s Drug Responses

Genetic research is also focusing on the genetic nuances that make one person exhibit specific symptoms and/or react to the same treatment differently from the next. Scientists are categorizing patterns of genetic variation (SNPs and haplotypes, as discussed earlier) that correspond to distinct symptoms and responses.

Eventually, medical interventions will be based on individualized risk assessment derived from these genetic differences. Future doctors will custom-select drug treatments based on an evaluation of medically significant areas of a patient’s genome, a field called pharmacogenetics. Currently, most of our medical prescriptions operate on a “one size fits all”—and sometimes a “hit or miss”—basis. For a certain disease, we all receive a similar medication at a similar dose. However, some prescriptions provide optimal benefits for a fraction of patients, while the rest receive sub-optimal or no benefits, or suffer serious side-effects. An estimated 100,000 people die each year, and 2.2 million suffer serious reactions, from medications that
are generally considered safe\textsuperscript{4}. Much of these differences in drug response is attributed to variations in the genes involved in metabolizing drugs or cellular sensitivity to drugs. Ideally, pharmacogenetics will allow doctors to scan a patient’s genetic profile for medically significant variations before prescribing a specific drug and dosage.

Cancer diagnostics are already moving in this direction. In breast cancer, for example, genetic tests of tumor cells help doctors determine which chemotherapy regimen to begin. If a tumor cell carries a mutation called HER2, the tumor cells produce abnormal amounts of a receptor protein that makes the cell susceptible to the drug Herceptin. Herceptin latches on to those receptors and disrupts the cell’s signal to continue dividing, causing the tumor to shrink. If the tumor does not carry that mutation, the cancer will not respond to Herceptin and the woman needs another form of chemotherapy. Likewise, scientists have recently correlated markers in cancer cells with their tendency to metastasize and spread to other tissues. By examining the RNA produced in the cell, researchers can determine whether genes that cause metastasis are turned on. Those results can guide doctors in their choice of cancer treatments.

Cancer is the first area where genomic technology helps tailor a treatment based on an individual’s genetics. Eventually, pharmacogenetics may enhance even the most routine medical treatments.

### The Future of Genetic Applications to Medicine

Substantial challenges in bringing the Human Genome Project to full fruition remain, but advances in early intervention, preventive strategies and personalized medicine will begin to alleviate some of the current issues and patient concerns. The ability to learn about our genes will affect the standards of medical care and it will facilitate preventive health care. However, the use of the information will depend on the individual and their health care professionals. Greater public and professional understanding of genetics will dramatically increase the beneficial and effective application of genetic medicine. Accurate transmission of complex information and a clear understanding of the implications of that information will be critical to the transfer of genome discoveries to human health.

Basic research in genetics continues to provide greater understandings of disease processes and advance our ability to test for diseases, intervene early in a disease, and provide better medical outcomes. This progress should put genetic testing and

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personalized, preventive medicine to beneficial use for greater numbers of people.

We have come a long way since Watson and Crick’s discovery of the structure of DNA in 1953. Despite the giant strides that have been made, understanding how variations in our DNA affect our health is still a work in progress. Future basic research will definitely reveal more about the information treasure contained in our genomes. Mining this treasure will benefit every one of us as well as humanity.

Biographies

Cathryn M. Delude writes about science, medicine, biotechnology, water, and energy from Andover, Massachusetts. She develops science education materials with The Writing Company and has written for the Howard Hughes Medical Institute, the Boston Globe, Your World Magazine: Biotechnology and You, Nature Biotechnology and other publications.

Joann Boughman, Ph.D. is the chief executive officer of the American Society of Human Genetics (ASHG), as well as Adjunct Professor of Obstetrics/Gynecology and Pediatrics at the University of Maryland, Baltimore (UMB). Dr. Boughman is a Board certified Medical Geneticist and was elected to the Board of Directors for the American Board of Medical Genetics in 1990. She is a registered Medical Technologist and a Founding Fellow of the American College of Medical Genetics. Dr. Boughman served on the Secretary’s Advisory Committee on Genetic Testing (SACGT), chairing the Education Workgroup for that committee. She also chairs the Molecular and Clinical Genetic Devices Panel of the Food and Drug Administration and is a Commissioner of Higher Education for the State of Maryland. Additionally, Dr. Boughman has performed research in population genetics and epidemiology of blindness and hearing impairments, congenital heart malformations and periodontal disease.

Selected Publications


